VOL. XVII NO. 6
JUNE 1958

Circulation

FICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

31st Scientific Sessions of the American Heart Association
San Francisco, Calif., from October 24-26, 1958
Deadline for Abstracts June 13, 1958

BOSTON UNIVERSITY
COLLEGE OF LIBERAL ARTS
LIBRARY

Published by Grune & Stratton, Inc.

"...the most satisfactory form of treatment to date."[1]

Only 5 per cent of patients in severe coronary shock survive with conventional treatment. With Levophed 1 out of 3 patients will be saved.[2]

1. Briller, S. A.: *M. Clin. North America* 41:619, May, 1957.
2. Tainter, M. L.: *Bol. Asoc. méd. Puerto Rico* 47:305, Aug., 1955.

sixfold increase in survival rate with life-saving Levophed®

bitartrate

natural ***antishock*** *pressor hormone*

Winthrop LABORATORIES New York 18, N.Y.

8238M

Levophed (brand of levarterenol), trademark reg. U. S. Pat. Off.

Circulation
JUNE 1958
VOL. XVII NO. 6
OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

Editorial

Anomalous Coronary Arteries with Special Reference to Arteriovenous-like Communications

ANOMALIES of the coronary arteries have generally been classified on anatomic rather than on functional grounds. This has led to separation of several anatomic entities which, from a functional viewpoint, should be brought together. The most important anomalies of the coronary arterial system, regardless of their anatomic details, have in common the features of arteriovenous-like communications. Recognition of this fact should lead to a more realistic approach in the functional evaluation of these anomalies and thence to the inevitable uniformity in principle regarding definitive surgical therapy.

The anomalies of the coronary arterial system fall into 3 major groups. The first group represents those anomalies that, under usual circumstances, are of minor significance. The second group is composed of coronary anomalies secondary to the effects of certain primary cardiac malformations. The third group includes anomalies that are not secondary to other conditions and that are of primary and major significance.

The coronary anomalies of minor significance involve those conditions in which the coronary arterial system arises entirely from the aorta and in which the ramifications of the arteries make no unusual communication with the cardiac chambers, the coronary veins, or the pulmonary trunk. In this group are such anomalies as both coronary arteries originating above one aortic sinus, the left circumflex artery originating from the right coronary artery, and the several varieties of single coronary artery. It is well to emphasize that a congenitally single coronary artery is capable of supplying adequately the entire heart, unless, by chance, it becomes the site of acquired disease.[1]

Though the function of the coronary arterial system is essentially normal in patients with these minor anomalies, peculiar courses of the vessels may be responsible for troublesome surgical problems when the anomalies happen to co-exist with certain intracardiac malformations. This is true in some patients with ventricular septal defect, but it is even commoner among patients who have ventricular septal defect associated with pulmonary stenosis (tetralogy of Fallot).

In an occasional case of this type the origin of one coronary artery may be stenotic or atretic. Under these circumstances the other coronary artery sends wide collateral branches to the coronary arterial bed of the stenotic or atretic artery. The troublesome aspect is that some of these branches extend across the anterior aspect of the right ventricle. Because of their location they may interfere with performance of right ventriculotomy and may introduce problems in performance of procedures designed to relieve infundibular stenosis.

The rare secondary anomalies of the coro-

From the Section of Pathologic Anatomy, Mayo Clinic and Mayo Foundation, Rochester, Minn.

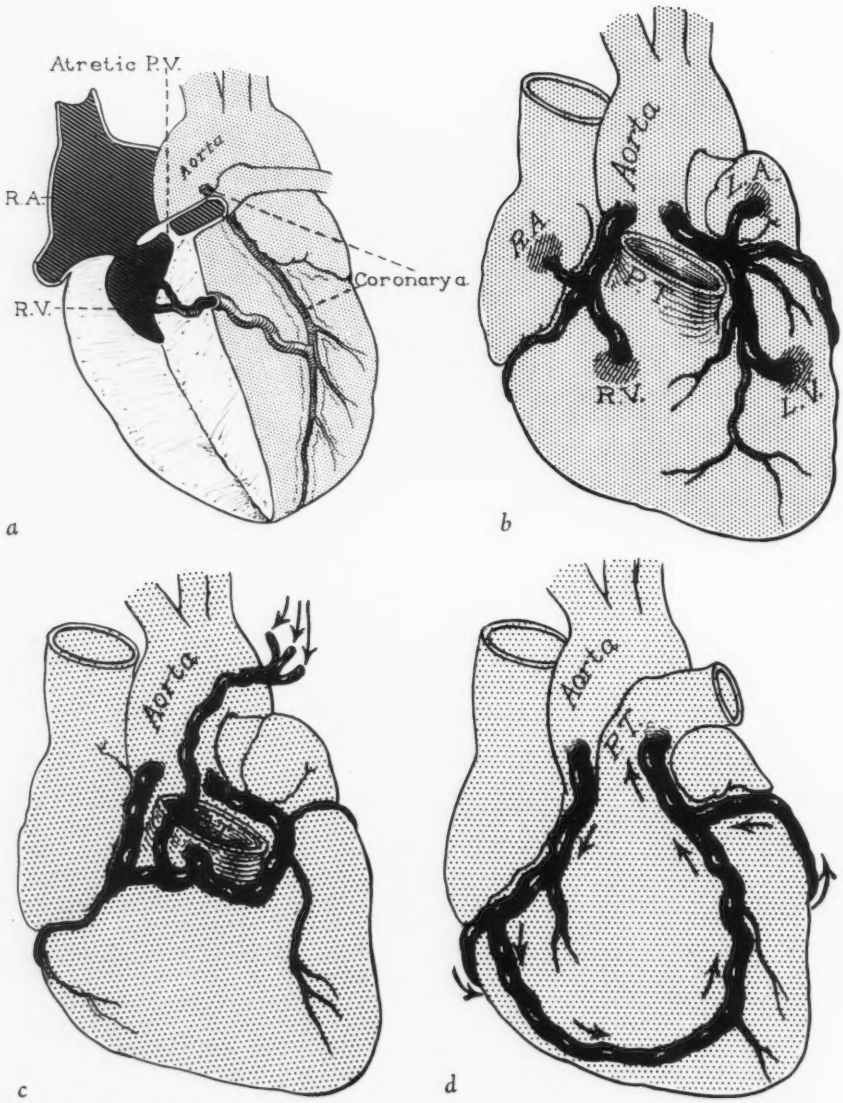


FIG. 1*a*. Secondary anomaly of the coronary system. There is atresia of the pulmonary valve. The ventricular septum is intact. Under these circumstances, and when the tricuspid valve is competent, sinusoids carry blood from the right ventricular cavity and converge to form a vessel that communicates with the aortic coronary arteries. A similar situation applies when the aortic valve is atretic and the ventricular septum is intact and associated with a competent mitral valve. In that instance, the anomalous coronary vessels leave the left ventricle.

b. Major anomalies of the coronary arteries represented diagrammatically. Sites of communication of coronary arteries with cardiac chambers are portrayed. The termination of the right coronary artery into right-sided chambers, and of the left coronary artery into left-sided chambers is simply displayed for diagrammatic convenience. Either of the coronary arteries may communicate with any of the cardiac chambers.

c. Anomalous communication of coronary arteries arising from the aorta with the pulmonary

nary arterial system are observed in cases of congenital atresia of either the aortic or pulmonary valve in the presence of an intact ventricular septum and of a competent corresponding atrioventricular valve. Such a case was described for the first time, as far as I am aware, by Blakeway[2] in 1918. Under these circumstances blood entering the ventricle proximal to the atretic semilunar valve cannot escape in either a forward or a backward direction. It is driven from the ventricle through myocardial sinusoids toward the epicardium (fig. 1*a*). In the peripheral aspect of the myocardium the enlarged sinusoids converge to form a gross vessel that emerges from the ventricular myocardium into the epicardium, where it unites with branches of the coronary arteries.[3] Anomalies of the secondary type, while of considerable interest to students of embryology of the coronary circulation, are, nevertheless, only of incidental significance in hearts with serious and underlying malformations.

The anomalies of major significance have varied anatomic patterns; but all have in common the functional characteristic of abnormal communication of the coronary arterial system with its high pressure on one hand and a cardiac chamber or vessel with either constant or intermittent low pressure on the other. This naturally sets the stage either for a true arteriovenous shunt or a shunt that is arteriovenous-like in nature. This functional disturbance makes the patient susceptible to cardiac failure, myocardial ischemia, and bacterial endarteritis. In isolated instances, surgical interruption of the shunt has been successfully accomplished.[4-9]

The major anomalies of the coronary arterial system may be subdivided anatomically into 2 groups depending on the site that is anomalously connected with the coronary arterial system, as follows (figs. 1*b* and *c*); (1) communication of the coronary arterial system with the right side of the circulation, including the coronary sinus or a tributary vein thereof, the right atrium, the right ventricle, or the pulmonary trunk, yielding a left-to-right shunt that is demonstrable both by cardiac catheterization[10] and by aortography,[8] and (2) anomalous communication of the coronary arterial system with the left atrium or ventricle, causing a functional disturbance similar to that of aortic insufficiency.

In each of these conditions there is tortuosity and dilatation of the portion of the coronary arterial system which is part of the abnormal communication. The generalized dilatation, at times, becomes complicated by formation of a localized saccular aneurysm. The latter feature, especially, and the uniform dilatation, to some extent, have been overemphasized in many reports on these conditions and the primary problem, that is, the arteriovenous communication, has been given secondary consideration. This practice also is responsible for the misleading titles of a number of reports that, although primarily concerned with anomalous arteriovenous communications, have titles that solely concern or prominently display such terms as "coronary aneurysm" or "congenital coronary aneurysm." The reader will realize that arterial dilatation is simply a feature common to all arteries proximal to abnormal arteriovenous communications. It is recognized that the literature contains reports of coronary arterial aneurysms that are claimed simply to be examples of localized arterial disease on a congenital basis. In some of these reports the picture as presented is consistent with that of an anomalous communication although no

trunk. In some instances, both coronary arteries make such a connection, while in others, only one coronary artery does so. Mediastinal vessels may join in the anomalous communication. These are represented by cut ends of vessels below the arrows.

d. Anomalous origin of one coronary artery from the pulmonary trunk while the other artery arises from the aorta. Displayed are communications between branches of the 2 arteries. It is through such communications that blood derived from the aorta is considered to enter the coronary artery that arises from the pulmonary trunk, and through the latter coronary artery, aortic blood is shunted into the pulmonary trunk.

such communication is described. One needs to recognize that the dramatic appearance of an aneurysm involving a coronary artery might draw the examiner's attention away from a search for an additional (and underlying) lesion in the form of an abnormal communication. In some instances a ruptured aortic sinus aneurysm may be confused with an anomalous communication of a coronary artery with a cardiac chamber.

Some further remarks are pertinent concerning the anatomic details of those anomalies that involve communication between a coronary artery and the pulmonary trunk.

Anomalous connection of the coronary arterial system with the pulmonary trunk takes 1 of 2 forms. The less common form is that in which the 2 coronary arteries originate normally from the aorta and, in addition, an accessory coronary artery arises from the pulmonary trunk as described by Krause[11] and in case 2 of Brooks'[12] report. The latter vessel makes gross communication with the proximal portions of one or both aortic coronary arteries, either directly[13] or through a plexus of vessels situated at the anterior aspect of the base of the heart (fig. 1*c*).

It is now generally agreed that in these cases the abnormal communication is associated with an arteriovenous-like condition in which there is a left-to-right shunt from the coronary arteries to the pulmonary trunk. In some cases mediastinal arteries also join in the anomalous communication and in the shunt, a condition noted by Björek and Crafoord[4] and in case 2 by Brooks.[12]

The commoner variety of anomalous communication between the coronary arterial system and the pulmonary trunk is the one usually classified as "anomalous origin of a coronary artery from the pulmonary trunk." In this type of anomaly only 1 of the 2 coronary arteries arises from the aorta while the other arises from the pulmonary trunk (fig. 1*d*). Often each of the 2 arteries is wider than normal, and tortuous. The reader who is under the influence of prevailing teaching may readily wonder why this condition should be classed as an arteriovenous communication.

The associated myocardial ischemia has been documented electrocardiographically many times since the report in 1933 of Bland, White, and Garland.[14] Nevertheless the cause of the myocardial ischemia has not met uniform recognition. The basis for disagreement revolves around the question, In what direction does the blood flow in the artery arising anomalously from the pulmonary trunk?

Currently what seems to be the view most commonly held is that blood flows *from the pulmonary trunk* into the anomalous coronary artery and thence to the myocardium. Indirect evidence for rejecting this theory is supplied by cases of cyanotic congenital cardiac disease. In some of these cases the level of oxygen saturation of the arterial blood is far below that of the venous blood of patients without right-to-left shunts. Yet cyanotic patients do not manifest clinical or pathologic signs of myocardial ischemia. Those who hold this view would answer this argument with the point that it is not so much the level of oxygen saturation but the low perfusion pressure supplied to the anomalous artery by the right ventricle and the pulmonary trunk that makes the myocardium ischemic.

My associate, Dr. H. B. Burchell, and I[15] have been more attracted by the theory that blood flows from the anomalous coronary *into the pulmonary trunk*. In regard to the latter theory H. St. John Brooks,[12] Demonstrator of Anatomy in Trinity College, Dublin, reported in 1886 on finding, in a dissecting room specimen (case 1), the origin of the right coronary artery from the pulmonary trunk while the left coronary artery arose normally from the aorta. Brooks noted that branches of the anomalously arising right coronary artery anastomosed, over the cardiac wall, with branches of the normally arising left coronary artery. His consideration of the direction of blood flow in the anomalous right coronary artery is significant and of historic importance. It is quoted as follows:

"A consideration of this case will show that a very interesting question is connected with it. Here are two arteries belonging to the different circulations—the pulmonary and the

systemic—anastomosing with each other. In these circulations, as is well known, the arterial pressure is very much greater in the systemic than in the pulmonary; how then did the blood flow in the anomalous coronary artery? There cannot be a doubt that it acted very much after the manner of a vein, and that blood flowed through it towards the pulmonary artery, and from thence into the lungs."

In 1927 Maude Abbott,[16] in describing the case of a 60-year-old woman with origin of the left coronary artery from the pulmonary trunk, agreed with Brooks' suggestion regarding direction of blood flow in the anomalous artery.

The following statements from several sources provide evidence that supports the view that blood in the anomalous artery is derived from the coronary artery that arises from the aorta and, further, that the blood then flows into the pulmonary trunk:

1. In both normal and anomalous arteries, anastomoses exist between branches of the 2 coronary arteries.

2. In the anomaly under consideration both coronary arteries have been observed to be extremely dilated and tortuous in a manner similar to what occurs in other situations in which arteriovenous communications are known to be present.

3. Clinical evidence of myocardial ischemia is usually not apparent until several months after birth, when the adult type of difference between systemic arterial and pulmonary arterial pressures becomes established. At this time the maximal tendency for flow of blood from the artery arising from the aorta into branches of the artery arising from the pulmonary trunk would be expected to become manifest.

4. Perfusion studies on postmortem specimens show evidence of free communication between branches of the 2 arteries[17, 18] and, through these pathways, communication of the aorta with the pulmonary trunk.

5. A fortuitous observation was made by Apley and associates[19] that when the coronary artery that arose from the pulmonary trunk was divided at operation, bright red blood flowed freely from its distal end.

Thus in anomalous origin of 1 coronary artery from the pulmonary trunk, not only theory but also observations are in strong support of the concept that there is run-off of blood from the normally arising artery into the anomalous one, and thence *into* the pulmonary trunk. Anomalous origin of a coronary artery from the pulmonary trunk, therefore, logically seems to be classed along with other anomalies in which an arteriovenous fistula-like condition exists and is undisputed.

JESSE E. EDWARDS

REFERENCES

1. ROBERTS, J. T., AND LOUBE, S. D.: Congenital single coronary artery in man: Report of 9 new cases, one having thrombosis with right ventricular and atrial (auricular) infarction. Am. Heart J. **32**: 188, 1947.
2. BLAKEWAY, H.: A hitherto undescribed malformation of the heart. J. Anat. **52**: 354, 1918.
3. WILLIAMS, R. R., KENT, G. B., JR., AND EDWARDS, J. E.: Anomalous cardiac blood vessel communicating with the right ventricle: Observations in a case of pulmonary atresia with an intact ventricular septum. Arch. Path. **52**: 480, 1951.
4. BIÖRCK, G., AND CRAFOORD, C.: Arteriovenous aneurysm on the pulmonary artery simulating patent ductus arteriosus botalli. Thorax **2**: 65, 1947.
5. JOHNSON, J.: Quoted by Davis and associates.[6]
6. DAVIS, C., JR., DILLON, R. F., FELL, E. H., AND GASUL, B. M.: Anomalous coronary artery simulating patent ductus arteriosus. J.A.M.A. **160**: 1047, 1956.
7. MOZEN, H. E.: Congenital cirsoid aneurysm of a coronary artery with associated arterioatrial fistula, treated by operation: A case report. Ann. Surg. **144**: 215, 1956.
8. MORROW, A. G.: Personal communication.
9. GASUL, B. H., FELL, E. H., AND DILLON, R. F.: Personal communication.
10. DAVISON, P. H., MCCRACKEN, B. H., AND MCILVEEN, D. J.: Congenital coronary arterio-venous aneurysm. Brit. Heart J. **17**: 569, 1955.
11. KRAUSE, W.: Über den Ursprung einer akzessorischen A. coronaria aus der A. pulmonalis. Ztschr. rat. Med. **24**: 225, 1865.
12. BROOKS, H. ST. J.: Two cases of an abnormal coronary artery of the heart arising from

pulmonary artery: With some remarks upon the effect of this anomaly in producing cirsoid dilatation of the vessels. J. Anat. **20**: 26, 1886.

13. Baylis, J. H., and Campbell, M.: Unusual cause for continuous murmur. Guy's Hosp. Rep. **101**: 174, 1952.
14. Bland, E. F., White, P. D., and Garland, J.: Congenital anomalies of coronary arteries: Report of unusual case associated with cardiac hypertrophy. Am. Heart J. **8**: 787, 1933.
15. Edwards, J. E.: Symposium on cardiovascular diseases: Functional pathology of congenital cardiac disease. Pediat. Clin. North America **1**: 13, 1954.
16. Abbott, M. E.: Congenital Cardiac Disease. *In* Osler, William, Modern Medicine. Ed 3, Philadelphia, Lea & Febiger, 1927, vol 4, p. 794.
17. Kittle, C. F., Diehl, A. M., and Heilbrunn, A.: Anomalous left coronary artery arising from the pulmonary artery. Report of a case and surgical consideration. J. Pediat. **47**: 198, 1955.
18. Case, R. B., Morrow, A. G., Stainsby, W. and Nestor, J. O.: Anomalous origin of the left coronary artery: The physiologic defect and suggested surgical treatment. Circulation **17**: 1062, 1958.
19. Apley, J., Horton, R. E., and Wilson, M. D.: The possible role of surgery in the treatment of anomalous left coronary artery. Thorax **12**: 28, 1957.

Medical Eponyms

By Robert W. Buck, M.D.

Broadbent's Sign. Credit for the discovery of this sign must be given to Sir William Broadbent (1835-1907), although it was first described by his son, Walter Broadbent, in an article entitled "An Unpublished Physical Sign" which appeared in *The Lancet* for July 27, 1895, pages 200-201. Later in 1895 an elder son, John F. H. Broadbent, now Sir John, included a description of the sign in his book *Adherent Pericardium*, page 26, London, 1895. It was not until 1898 that Sir William published his description which appears under the title "Adherent Pericardium" in the *Transactions of the Medical Society of London* **21**: 109-122, London, 1898.

"A systolic tug of the left false ribs posteriorly communicated by the diaphragm may be conspicuous. The recoil from the drag may be so distinct as to look and feel to the hand like pulsation, and in the first case in which I observed it, now more than 20 years since—a case of left empyema—it was taken for pulsation, and it was supposed that a pulsating tumour of some kind underlay the empyema. A *post-mortem* examination showed that the cause was adherent pericardium. I have often seen this tugging since, and in some cases it can be made to affect the right false ribs by causing the patient in the sitting position to lean over to the left so as to throw the drag of the heart upon the right half of the diaphragm. It must be added that this indication is not infallible, as the tugging has been observed when the heart was hypertrophied without adhesions."

Observations on the Mechanism of Atrial Gallop Rhythm

By JAMES J. LEONARD, M.D., ARNOLD M. WEISSLER, M.D., AND JAMES V. WARREN, M.D.

An atrial gallop sound is a frequent finding in hypertensive cardiovascular disease, myocardial infarction, and in the presence of a prolonged atrioventricular conduction time. In view of evidence relating this sound to a ventricular pressure wave resulting from atrial contraction, modification of this hemodynamic event was studied by means of tourniquet pooling of blood in the extremities. In the 18 patients studied, this maneuver caused striking changes in the intensity and timing of the atrial gallop. Analysis of these changes helps explain the frequent appearance of this triple rhythm in severe hypertensive cardiovascular disease.

GALLOP rhythm is said to be present when an audible diastolic sound is added to the 2 normal heart tones. The atrial gallop is a low-pitched sound occurring after atrial systole, but before the subsequent ventricular contraction. This sound is frequently heard in patients with hypertensive cardiovascular disease, myocardial infarction, and in the presence of atrioventricular conduction disturbances (heart block, whether complete or partial).[1] It was thought that some information about the genesis of this sound might be obtained by altering intracardiac pressure relationships. This was accomplished by pooling of blood in the extremities through the use of occlusive venous cuffs.

MATERIALS AND METHODS

Eighteen hospitalized patients were studied. Seventeen were patients with hypertensive cardiovascular disease, either "essential" or renal in origin, but all either severe or malignant in nature. The systolic pressure was over 200 mm. Hg and diastolic pressure over 110 mm. Hg in all. The patients were not in obvious cardiac failure at the time of study, although many had previously been decompensated. All had roentgenographic or electrocardiographic evidence of left ventricular hypertrophy. One patient thought to have an atrial gallop sound from the right side of the heart had pulmonary hypertension due to sarcoidosis, but a normal systemic arterial pressure. Only patients with gallop sounds that were readily audible and with phonocardiograms free from extraneous vibrations were utilized. Because the patients were studied while they were lying quietly on a flat comfortable surface, those who were dyspneic, restless, or orthopneic could not be satisfactorily investigated.

All sound tracings were taken on the logarithmic scale of the Sanborn "Twinbeam" photographic recording instrument at a paper speed of 75 mm. per second. The standard 50-mm. open-bell chest piece was placed on the chest wherever the sounds to be investigated were best demonstrated. This was usually the apex or along a line drawn from the apex to the sternum at the level of the fifth interspace.

In many instances additional tracings were taken to record the linear or apex cardiogram with a piezo-electric crystal microphone. These vibrations were recorded simultaneously with and from the same chest piece as the logarithmic phonocardiogram.

In order to study the effect of peripheral blood pooling, pneumatic cuffs 6 inches wide were placed around all extremities. Care was taken to apply the cuffs as high as possible, yet not to cause discomfort. The cuffs were inflated simultaneously and rapidly to the level of 100 mm. Hg. The inflation was sustained for 5 minutes, and the cuffs then were released suddenly. Following control sound tracings recordings were made at minute intervals during the period of sustained inflation. The period during cuff release and 1 minute thereafter was also recorded.

RESULTS

Control phonocardiograms demonstrated the atrial gallop deflections usually 2 to 3

From the Department of Medicine, Duke University School of Medicine, Durham, N. C.

This research was supported in part by a research grant (H-1217), and a Traineeship (Dr. Leonard) from the National Heart Institute, National Institutes of Health, Public Health Service, and by a research fellowship (Dr. Weissler) from the American Heart Association, and by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command under contract No. AF18(600)1542.

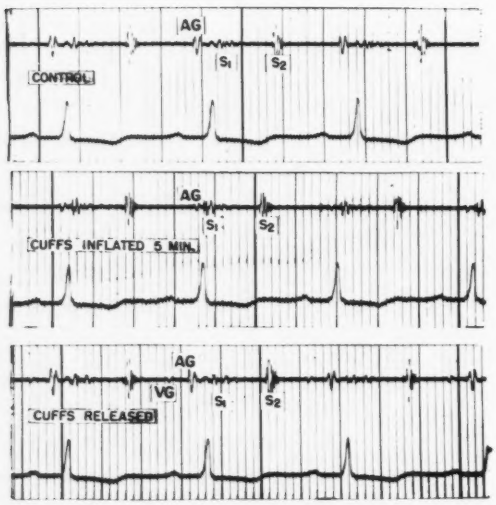


FIG. 1. Simultaneous logarithmic phonocardiogram and electrocardiogram displaying a prominent atrial gallop (*AG*) on the control tracing. This gallop sound decreased in amplitude and migrated toward the first heart sound after 5 minutes of cuff inflation. Upon release of cuffs, the atrial gallop returned to its original amplitude and position in presystole. With the sudden release of cuffs, a ventricular gallop (*VG*) appears for a few beats.

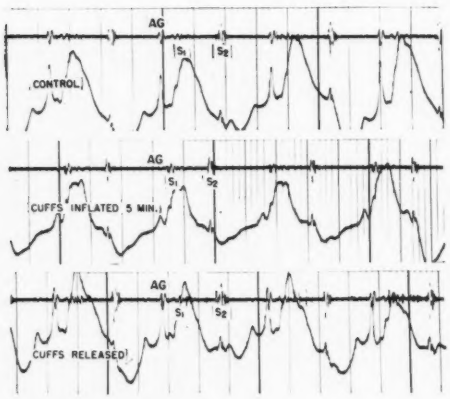


FIG. 2. Simultaneous logarithmic phonocardiogram and apex cardiogram demonstrating on the control tracing a prominent atrial gallop sound (*AG*). The apex cardiogram displays a sharply pointed precordial wave synchronous with the sound. After 5 minutes of venous pooling the gallop sound decreased strikingly in intensity and moved closer to the first heart sound. Similar changes occurred in the apex cardiogram. After release of cuffs the atrial gallop and its respective precordial wave returned to their control amplitude configuration and time relationship.

cycles in duration, occurring late in diastole, 0.07 second or more before the onset of the first heart sound. Such deflections occurred between the inscription of the P wave and QRS of the electrocardiogram (fig. 1). In addition, apex cardiograms demonstrated prominent, sharply peaked presystolic waves, the peaks of which were simultaneous with the gallop sound deflections (fig. 2).

Upon inflation of the venous occlusive cuffs, the gallop sound moved progressively toward the first heart sound (fig. 1). The average migration in the 18 cases studied was 0.034 second, with a range of 0.016 to 0.060 second. As this movement progressed, the gallop sound completely disappeared in 6 cases, diminished to less than 50 per cent of its control magnitude in 6 cases, and remained essentially unchanged in amplitude in 6 cases. With cuff inflation, there was concurrent migration of the atrial gallop wave of the apex cardiogram toward the first sound, its peak remaining synchronous with the gallop sound (fig. 2). The amplitude of the wave diminished and its summit was no longer sharp, but became rounded and less conspicuous. With release of cuffs, sound and apex tracings returned to their control configuration and temporal relationships (figs. 1 and 2).

In many of the patients the first sound was not so loud as the second heart sound at the apex. In 6 instances there was a definite increase in intensity of the first heart sound as the atrial gallop migrated into its initial deflections (fig. 3). In many, the deflections of the atrial gallop that had occurred before the onset of the QRS in the control tracings were now present as small slow vibrations, occurring just before the early rapid vibrations of the first sound during the inscription of the R wave (fig. 3). Upon sudden release of cuffs these low-frequency sounds migrated back into their former position in presystole (fig. 3).

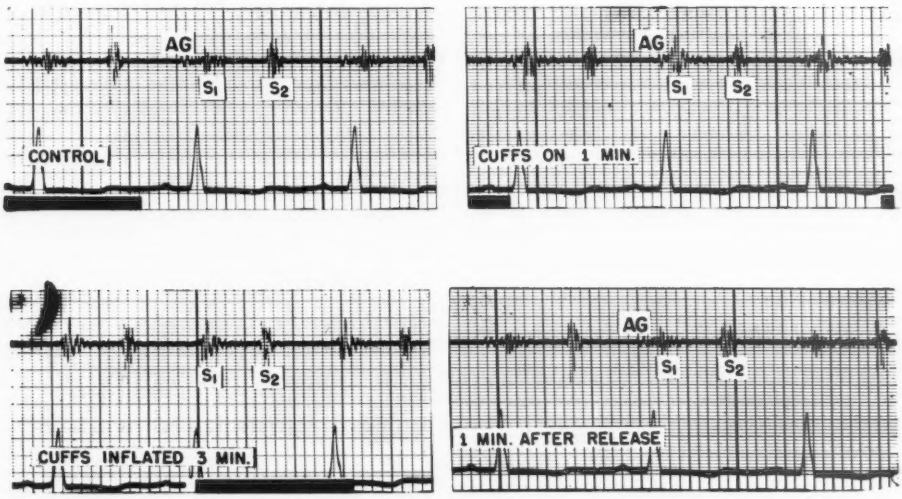


FIG. 3. Phonoeardiogram showing atrial gallop rhythm on the control tracing. After 1 minute of venous pooling by cuffs the gallop deflections migrated toward the first heart sound and appeared as low-frequency vibrations after the onset of the R wave. After 3 minutes of pooling the atrial sound disappeared. Upon release of cuffs the atrial sound returned to control amplitude and time relationship.

DISCUSSION

The audible atrial gallop sound does not occur synchronously with mechanical atrial systole.[1] This sound occurs simultaneously with a pressure wave appearing in the ventricle as a result of atrial contraction. Such a presystolic ventricular pressure wave can be demonstrated by electrokymograms, which show an outward movement of the ventricular wall at this time,[2] and apex cardiograms, which show a precordial thrust, the peak of which is simultaneous with the gallop sound. Ballistocardiograms under such circumstances reveal ventricular forces directed headward and to the right, the onset of which are synchronous with the gallop sound.[3, 4] It is true that at the time of mechanical atrial systole, vibrations occur that may be graphically recorded when the pickup is in the esophagus[5] or in the atrial cavity.[6] Recording instruments sensitive in the low frequencies (stethoscopic scale of Rappaport and Sprague;[7] medium and low frequency of Leatham[8]) may register these sounds over the precordium. These vibrations do not represent the audible atrial gallop sound heard by the clinician. In the past failure to differentiate these subaudible vibrations from sounds audible to the human ear has resulted in confusion regarding the timing of the atrial gallop.

It is well recognized that atrial gallop sounds may be heard in patients with heart block when atrioventricular conduction time is prolonged. Under these circumstances the vibrations related to atrial contraction precede the first heart sound by an interval long enough to render the atrial component audible as a separate sound (fig. 4*c*). The audibility is favored by the fact that the first heart sound itself is relatively faint when the P-R interval is prolonged.

The atrial sound may be frequently heard in additional patients with cardiovascular disease, even in the presence of a normal P-R interval[1] (fig. 4*d*). In particular, patients with hypertensive cardiovascular disease are frequently found to have a readily audible atrial gallop sound. It is in this type of patient that tourniquet application has been observed to produce the changes reported here.

Numerous investigators have studied the

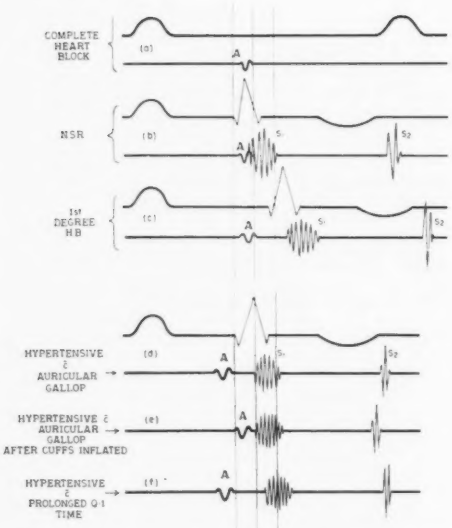


FIG. 4. (*a*). Complete heart block with audible atrial sound (*A*). (*b*). Normal sinus rhythm with atrial sound (*A*) lost in the first heart sound. (*c*). First degree heart block; atrial sound (*A*) becomes audible when the first heart sound is delayed by the A-V conduction defect. (*d*). Hypertensive cardiovascular disease and an audible atrial gallop (*A*) due to early appearance of the atrial sound. (*e*). Migration of the sound (*A*) toward the first sound after inflation of venous cuffs. (*f*). Enhanced audibility of the atrial gallop (*A*) by delay in onset of first sound due to prolonged Q-1 time.

hemodynamic effects of pooling blood by venous occlusive cuffs. In normal subjects the cardiac output decreases slightly.[9] A fall in central venous pressure occurs in association with a corresponding decrease in the pressures in the right atrium,[10, 11] right ventricle, pulmonary artery,[12] and the left atrium.[13] Thus, atrial systole results in somewhat less blood being ejected into the ventricle, which in turn is under less tension. Under these conditions the phenomena producing the atrial sound are altered so that it occurs later and often becomes faint or even inaudible. The peak on the apex cardiogram associated with the sound is also delayed and is usually decreased in magnitude. At this time the early vibrations of the first heart sound are apparently related to atrial activity, a point that has been debated in the literature.[14]

An additional factor that may enhance the audibility of the atrial sound in patients with hypertensive cardiovascular disease is the delay in the onset of the first heart sound, as demonstrated by slight, but significant, increase in the Q-1 interval* in the patients studied. The Q-1 time in the group was .066 ± .014 second, as opposed to a control group of 18 normal subjects in which the Q-1 time was .055 ± .01 second ($p < .01$). In the hypertensive group 7 patients had Q-1 times of .07 second or longer. This delay occurred in the absence of bundle-branch block, or a QRS complex longer than .10 second. The result of this increase in the Q-1 interval was to separate further the first sound from the atrial vibrations and thus aid in unmasking the atrial sound (fig. 4*f*).

To this point we have not discussed what structure, when displaced by the pressure wave, actually produces the sound. The 2 most widely held theories are that the sound is caused by vibration of the ventricular musculature, or that a tensing or even reclosure of the valves takes place at this time. It is generally accepted that valve leaflets can produce a sound, but whether or not an audible sound can emanate from the ventricular musculature is debated.[4] Henderson and Johnson,[15] as well as Dean,[16] using excised hearts and models showed to their satisfaction that valves may tense or reclose after atrial systole. Little[17, 18] has shown in dogs that following atrial contraction, there is increased pressure in the ventricle. As atrial relaxation occurs and pressure in the atrium drops, that in the ventricle still elevated by the effects of atrial contraction may exceed it in late diastole before subsequent ventricular systole. Such a reversal of the diastolic atrioventricular pressure gradient could result in valve reclosure. The hemodynamic effects of tourniquet application may well alter these pressure relationships and lead to loss of the atrial sound.

The available information indicates, therefore, that an audible atrial gallop may occur

*Time from the onset of the Q wave of the electrocardiogram to the onset of the first major vibrations of the first heart sound.

nder several possible circumstances. When onduction from atrium to ventricle is deayed, as in heart block, atrial contraction vith its augmentation of ventricular filling roduces a sound in late diastole before the nset of ventricular contraction. Here temoral splitting off of the atrial sound occurs s the result of the separation of atrial and entricular activity by the conduction defect. n other patients the sound may occur with ormal conduction times when the pressure ave resulting from atrial activity appears to e transmitted more rapidly to the ventricle. As a result the sound occurs early and preedes the first sound by a time interval adequate to render it acoustically separate. Pooling of blood in the extremities results in modification of pressure volume relationships in such a way that the transmission of the wave is progressively slowed and the resulting sound migrates back toward the first heart sound. In some patients delay in onset of the first sound (prolonged Q-1 time) may enhance the tendency toward gallop production.

Summary

The effect of tourniquet pooling of blood with resultant lowering of intracardiac pressures has been observed in a group of patients with readily audible atrial gallop rhythm. A progressive migration of the atrial gallop sound toward the first heart sound appeared, accompanied by a disappearance or striking decrease in the amplitude of the sound in two thirds of the cases. Apex cardiograms showed concurrent migration and diminution in the precordial atrial gallop wave.

Available evidence indicates that atrial gallop sounds may occur (1) when atrioventricular conduction is prolonged or (2) when altered ventricular pressure volume relationships result in an earlier atrial sound. In some instances, delay in onset of the first heart sound (prolonged Q-1 time) may enhance the tendency toward gallop production.

Summario in Interlingua

Un gruppo de patientes con facilemente audibile rhythmos de galopo atrial esseva studiate con respecto al effecto del reduction del pression intracardiac resultante de stagnation de sanguine sub le application de tourniquets. Appareva un migration progressive del sono de galopo atrial verso le prime sono cardiac, accompaniate per le disparition o un reduction frappante in le amplitude del sono in duo tertios del casos. Cardiogrammas apical monstrava simultaneitate de migration e diminution in le unda precordial de galopo atrial.

Le datos disponibile indica que sonos de galopo atrial pote occurrer (1) quando le conduction atrio-ventricular es prolongate o (2) quando alterationes del relation inter pression e volumine in le ventriculo resulta in un formation plus prompte del sono atrial. In certe casos, retardos in le declaration del prime sono cardiac (prolongation del tempore Q-1) promove possibilemente le tendentia al production del rhythmo de galopo.

REFERENCES

1. Weitzman, D.: The mechanism and significance of the auricular sound. Brit. Heart J. **17**: 70, 1955.
2. Kuo, P., Hildreth, E., and Kay, C.: The mechanism of gallop sounds studied with the aid of electrokymograms. Ann. Int. Med. **35**: 1306, 1951.
3. Dock, W., Mandelbaum, H., and Mandelbaum, R. A.: Ballistocardiography. St. Louis, C. V. Mosby Co., 1953.
4. —: Heart sounds, cardiac pulsations and coronary disease. Porter Lecture Series **21**: 35, 1956. Lawrence, University of Kansas Press.
5. Taquini, A. C., and Braun-Menéndez, E.: Constance du bruit auricularre par auscultation ou inscription oesophagienne. Compt. rend Soc. de biol. **120**: 728, 1935.
6. Lewis, D. H., Wallace, J. D., Deitz, G. W., and Brown, J. R., Jr.: Intracardiac phonocardiography in man. Symposium: Present status of heart sound production and recording. University of Buffalo, Feb. 14, 1957.
7. Rappaport, M. B., and Sprague, H. B.: The graphic registration of the normal heart sounds. Am. Heart J. **23**: 591, 1942.
8. Leatham, A.: Phonocardiography. Brit. M. Bull. **8**: 333, 1952.
9. Fitzhugh, F. W., Jr., McWhorter, R. L., Jr., Estes, E. H., Jr., Warren, J. V., and

MERRILL, A. J.: The effect of application of tourniquets to the legs on cardiac output and renal function in normal human subjects. J. Clin. Invest. **32**: 1163, 1953.

10. WARREN, J. V., AND STEAD, E. A., JR.: The effect of the accumulation of blood in the extremities on the venous pressure of normal subjects. Am. J. M. Sc. **205**: 501, 1943.
11. GAUER, O. H., HENRY, J. P., AND SIEKER, H. O.: Changes in central venous pressure after moderate hemorrhage and transfusion in man. Circulation Research **4**: 79, 1956.
12. DOYLE, J. T., WILSON, J. S., ESTES, E. H., JR., AND WARREN, J. V.: The effect of intravenous infusions of physiologic saline solution on the pulmonary arterial and pulmonary capillary pressure in man. J. Clin. Invest. **30**: 345, 1951.
13. HENRY, J., GAUER, O. H., AND SIEKER, H. O.: The effect of moderate changes in blood volume on left and right atrial pressures. Circulation Research **4**: 91, 1956.
14. COUNIHAN, T., MESSER, A. L., RAPPAPORT, M. B., AND SPRAGUE, H. B.: The initial vibrations of the first heart sound. Circulation **3**: 730, 1951.
15. HENDERSON, Y., AND JOHNSON, F. E.: Two modes of closure of the heart valves. Heart **4**: 69, 1912.
16. DEAN, A. L., JR.: The movement of the mitral cusps in relation to the cardiac cycle. Am. J. Physiol. **40**: 206, 1916.
17. LITTLE, R. C.: Effect of atrial systole on ventricular pressure and closure of the A-V valves. Am. J. Physiol. **166**: 289, 1951.
18. —, HELTON, J. G., AND SCHOEFER, R.: The first heart sound in normal and ectopic ventricular contractions. Mechanism of closure of the A-V valves. Circulation Research **2**: 48, 1954.

Dubois, E. L., Katz, Y. J., Freeman, V., and Garbak, F.: Chronic Toxicity Studies of Hydralazine (Apresoline) in Dogs with Particular Reference to the Production of the "Hydralazine Syndrome." J. Lab. & Clin. Med. **50**: 119 (July), 1957.

Ten dogs received hydralazine in varying dosages orally. The pattern and rate of toxic reactions varied directly with the dosage schedule. A progressive normocytic anemia, fever, anorexia, and cachexia appeared, often with terminal convulsions. Leukopenia was not apparent. LE cells were not found. Autopsy findings were compatible with a diagnosis of hemolytic anemia (i.e., congestion of the liver and spleen with hemosiderosis of both). No renal or other changes suggested systemic lupus erythematosus (SLE). From these experiments the authors concluded that hydralazine did not give rise to the SLE syndrome, and that in human beings there are 2 types of hydralazine reactions. The most common is a drug sensitivity in a patient with essential hypertension, the other type being a patient with latent SLE whose underlying disease is exacerbated by the use of hydralazine. In this latter type, the picture is typical of the underlying disease, and LE cells are found. The disappearance of symptoms and laboratory changes after withdrawal of a noxious agent in SLE is common.

MAXWELL

Osmotic Diuretic Treatment of Refractory Edema

By Lionel M. Bernstein, M.D., Ph.D., Bernard Blumberg, M.D., and Murray C. Arkin, M.D.

Many patients with edema of congestive cardiac failure, nephrosis, and cirrhosis become refractory to all diuretic therapy. Theoretically, the use in adequate dosage of osmotic diuretics whose action is dependent upon physical factors should augment sodium, chloride, and water excretion from whatever level exists prior to their use. In refractory edema, the effect of other diuretics (via alteration of the metabolic, actively resorbing mechanisms of the tubular cells) on tubular rejection of sodium, chloride, and water should be increased by osmotic diuretics. Mannitol was administered intravenously in large doses to test the effectiveness of osmotic diuretics in refractory edema.

OSMOTIC diuretics exert their action through physical rather than cellular metabolic effects.[1-3] Osmotic diuretic action depends upon the presence of nonabsorbable particles within the isosmotic proximal tubule. These nonabsorbable particles cause retention of water within the proximal tubule to maintain a constant *total* osmolar concentration of 310 mOsM. per L. As compared with the preosmotic diuretic baseline, the water that is so retained progressively dilutes the sodium in the fluid as it traverses the proximal tubule. Thus, an unchanged cell surface area containing the active metabolic sites for sodium resorption is exposed to a fluid of progressively lesser sodium concentration.[1] The absorbing sites being less saturated, less sodium particles are absorbed (despite unaltered avidity of the individual cell sites), and more sodium particles passed on distally. Within the proximal tubule the additional nonabsorbed sodium and accompanying anions behave as osmotic diuretic particles[4] and retain water that also is passed on distally. In the distal convoluted tubule, absolute quantities absorbed, even when maximal, are small fractions of the increased total quantities presented and explain the inability of the distal tubule greatly to modify the nature of the fluid presented to it.[1-3] Urine during such marked osmotic diuresis is similar to the fluid leaving the proximal tubule in total concentration, pH, and individual ion concentrations. During such osmotic diuresis, the administration of a hypertonic solution (such as 1500 mOsM. per L.) coupled with excretion of urine with a 300 to 350 mOsM. per L. concentration indicates a net loss of solute.

Osmotic diuretics have been tried in refractory edema, both successes[5,6] and failures[7] having been reported. However, the sparsity of data and the infrequency of their use suggest that they have not been generally effective. From theoretical considerations, the limiting factor for their effectiveness is the presence of an adequate filtration rate to allow enough osmotic diuretic particles to reach the tubular lumen. Mercurial and osmotic diuretics potentiate each other's effects.[5,8]

Mannitol, regarded as an almost inert, nontoxic hexose, excreted by glomerular filtration alone, is an osmotic diuretic available for parenteral injection. The experience with mannitol administered intravenously with and without a mercurial diuretic in the treatment of refractory edema is the basis of this report.

Methods

Subjects were chosen who had marked edema of nephrosis, cardiac failure, or cirrhosis that was refractory to dietary salt restriction (less than 500 mg. of sodium per day) plus the usual diuretics, singly and in combination. In all patients, use of mercurial diuretics, aminophylline, ammonium chloride, and Diamox was unsuccessful. In the 2 cardiac patients, digitalis was used for both; ACTH priming and alcohol were used for one (case 2). Because of prolonged refractory

From the Medical Service and the Medical Research Division, V.A.H., Hines, Ill.

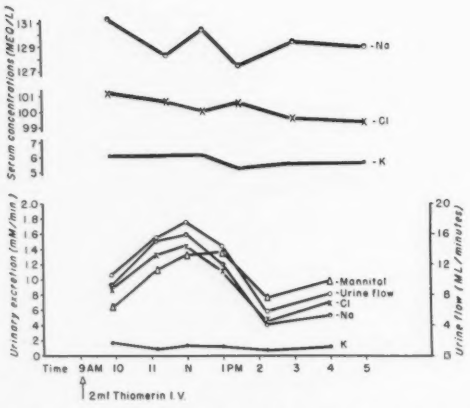


FIG. 1. Case 1, Exp. D., nephrotic edema. Serum electrolyte concentrations and urinary excretion rates of sodium, potassium, chloride, mannitol, and water during mannitol-Thiomerin treatments.

edema, diuresis with mannitol* administered intravenously, was attempted. The dietary sodium content was constant for several weeks before, during, and after mannitol administration in all cases. Water intake was ad libitum. Patients were treated with infusions of 25 per cent mannitol intravenously in amounts up to 2,000 ml. (500 Gm.) over periods of 4 to 8 hours. Usually a priming dose was followed by a slower infusion. Interruptions of the infusions occurred occasionally. As far as possible, after initial exploratory experiments on 1 patient, a standard approach was roughly followed. Daily outputs of water, sodium, potassium, and chloride were determined immediately before, during, and immediately after administration of mannitol. When mannitol and a mercurial diuretic were given together, the outputs were compared with those without treatment, and with mercurial diuretic treatment alone.

A mercurial diuretic (Thiomerin) was given intravenously as single 2-ml. doses, or as 2 1-ml. doses 3 to 5 hours apart. In several cases, urinary specific gravity and the rate of urine flow (for 10- to 60-minute periods) were measured throughout the course of mannitol administration. In 1 case, the excretions of mannitol, water, and electrolytes were measured during the course of a day of mannitol plus mercurial treatment.

Urinary creatinine excretions were measured by the method of Bonsnes and Taussky.[9]

Sodium and potassium were analyzed with the Perkin-Elmer flame photometer;[10] chloride by the method of Sendroy, as modified by Van Slyke and Hiller,[11] and mannitol by the method of Corcoran and Page.[12] Freezing point determinations were performed with the Fiske osmometer, by means of a sodium chloride standard curve.[13]

*The mannitol used in this study was provided by Merck, Sharp and Dohme, Rahway, N. J.

RESULTS

Treatment of Nephrotic Edema. The initial, exploratory studies were made on a patient with refractory nephrotic edema of several months duration (case 1, table 1). Intravenous administration of 100 to 200 Gm. of mannitol with and without 2 ml. of Thiomerin suggested (1) that mannitol alone caused greater water as compared with sodium loss than did Thiomerin alone (Exp. A and C, table 1); (2) that mannitol combined with Thiomerin caused much greater water and sodium losses than did either alone (Exp. A); and (3) that combined mannitol and Thiomerin administration significantly increased water and sodium excretion above control nontreatment levels (Exp. B and C).

Following a 2-week period without treatment, a critical test was performed. Excretions were studied for each of 5 consecutive days on which there were, respectively, no treatment, 2 ml. of Thiomerin, 2 ml. of Thiomerin plus 250 Gm. of mannitol, 2 ml. of Thiomerin, and no treatment (Exp. D, table 1). The sodium excretion on the mannitol plus Thiomerin day was increased 480 mEq. above the average of the days immediately preceding and following with Thiomerin alone. Generally, chloride excretion followed sodium excretion as the major accompanying anion. Potassium excretion was not altered by mannitol or Thiomerin administration or both. Total daily urinary output was increased about 800 ml. per day by Thiomerin as compared with no treatment; it was increased an additional 5,600 ml. by the administration of 250 Gm. of mannitol (in 1000 ml. of water) with Thiomerin. Figure 1 shows the rates of excretion per minute during the mannitol plus Thiomerin treatment day. The parallelism of sodium, chloride, and mannitol excretions (in milliosmoles per minute) and urine flow rates is clear. The failure of potassium excretion to increase during the osmotic di-

TABLE 1.—*Response of Refractory Edema Cases to Intravenously Administered Mannitol and Mercurial Diuretics*

	Day	Treatment		Volume (ml./day)	Urine				Body weight (lbs.)	Weight change per day (lbs.)
					Total amounts/day					
		Thiomerin (ml.)	Mannitol (Gm.)		Na(mEq.)	K (mEq.)	Cl (mEq.)	Creatinine (Gm.)		
Case 1										
Exp. A	1	–	100	3 260	75.0	89.6	105.6	1.83	188	−2
	2	2	100	5,120	297.0	89.1	366.3	1.54	186	−2½
	3	2	—	1,990	84.6	60.1	100.6	1.47	183½	−1
	4	–	–	–	–	–	–	–	182½	–
Exp. B	7	–	–	1,480	35.5	74.9	31.9	1.04	176	+1
	8	2	200	4,725	224.0	106.8	181.5	1.32	177	−1
	9	–	–	2,480	54.8	98.0	32.5	1.49	176	0
	10	–	–	–	–	–	–	–	176	–
Exp. C	11	–	–	1,915	49.4	78.5	21.1	1.39	176	−½
	12	–	200	4,485	77.1	110.3	54.9	1.44	175½	−1½
	13	2	100	3,810	133.0	102.5	137.1	1.52	174	−1
	14	2	–	1,250	24.8	55.6	13.7	1.13	173	+1
	15	–	–	–	–	–	–	–	174	–
Exp. D	27	–	–	2,235	87.8	104.2	94.0	1.20	178	+½
	28	2	–	3,440	259.0	98.4	275.0	1.03	178½	−2½
	29	2	250	8,685	660.3	106.0	639.1	1.56	176	−8½
	30	2	–	2,555	97.1	88.4	92.5	1.02	167½	−½
	31	–	–	2,060	39.8	96.0	28.6	1.15	167	+2
	32	–	–	–	–	–	–	–	169	–
Case 2										
	1	–	–	1,360	6.6	93.2	58.0	1.58	198½	−½
	2	2	–	1,980	75.2	159.0	149.0	2.34	198	−1
	3	2	400	6,620	264.0	210.8	254.4	2.11	197	−8½
	4	2	–	1,460	.0	20.7	2.1	1.46	188½	+½
	5	–	–	1,820	.0	30.4	.0	2.55	189	+2
	6	2	–	940	.3	6.0	1.2	1.69	191	0
	7	2	440	7,020	82.5	139.5	193.8	2.11	191	−4½
	8	2	–	1,440	.0	19.2	25.4	1.44	186½	+½
	9	–	–	1,400	.4	57.1	.5	3.25	187	0
	10	–	–	–	–	–	–	–	187	–
Case 3										
	1	2	–	1,120	15.6	53.1	62.7	.35	175	0
	2	2	–	1,500	13.4	68.0	51.4	.90	175	−2½
	3	2	350	8,060	356.8	152.0	465.0	.85	172½	−9½
	4	2	–	1,140	4.0	51.4	20.6	1.02	163	+3½
	5	–	–	600	.4	54.6	1.6	.84	166½	+1
	6	2	–	1,780	22.8	133.9	30.9	1.14	167½	+½
	7	–	–	–	–	–	–	–	168	–
Case 4										
	1	–	–	990	1.2	27.1	6.8	.79	153	−1
	2	2	–	1,800	52.4	63.4	92.2	.90	152	−2
	3	2	475	8,075	469.1	86.0	459.5	.49	150	−17½
	4	–	–	1,270	.8	36.4	–	.53	132½	+1½
	5	2	–	1,100	9.9	86.6	–	.12	134	0
	6	–	–	–	–	–	–	–	134	–

uresis is also evident. During this diuresis, there were no clinically significant changes in serum electrolyte levels.

Table 1 reveals daily body weight losses up to only 2½ pounds despite urinary volumes up to 5 L. per day in experiments A to C, indicating possible incomplete control of this ambulatory patient's water (and salt) intake. In experiment D, the massive output of water and sodium on Thiomerin plus mannitol treatment was accompanied by an 8½-pound loss. During the course of this treatment day, the gross edema of penis, scrotum, and lower extremities could be seen to disappear gradually, there remaining only a trace of edema at the end of the treatment day. Thirst was excessive throughout treatment. The combined mannitol and Thiomerin treatment effected great loss of water, sodium, and chloride, without adverse effects.

Treatment of Cardiac Edema. Two cases of refractory cardiac edema were treated with mannitol plus Thiomerin. The first (case 2) was a patient with primary pulmonary hypertension in a state of extreme, hopeless decompensation refractory to treatment for several months. The first control day studied revealed an output of only 6.6 mEq. of sodium, and 1,360 ml. of water (table 1). Thiomerin alone increased the sodium output to 75 mEq. and the urine volume to 1,980 ml., whereas Thiomerin plus 400 Gm. of mannitol increased the sodium excretion to 264 mEq., and the urine volume to 6,620 ml. This large urinary output was accompanied by an 8½-pound weight loss, despite which the patient's clinical condition improved negligibly. Following this, the urinary excretion of sodium fell to zero, whether or not Thiomerin was given. A second trial on Thiomerin plus 440 Gm. of mannitol increased the sodium output from zero to 82.5 mEq. with a urinary volume of 7,020 ml. per day, and caused a 4½-pound weight loss, again with very minor clinical improvement.

In this patient, potassium excretion was clearly and significantly elevated by the Thiomerin-mannitol treatment. Chloride excreting generally increased when potassium and sodium excretions increased.

The weight losses were rough measures of edema loss. The cardiac failure of this patient was not secondarily aggravated by the accumulated peripheral edema. Mobilization and excretion of this edema, while relieving the patient of some discomfort, did not basically alter his state of cardiac decompensation. There was definite, increased pulmonary congestion and dyspnea during the mannitol infusions related to an increase in extracellular fluid and blood volumes. The rate of mannitol infusion was decreased as pulmonary congestion increased. Pulmonary congestion was decreased within an hour after discontinuation of mannitol infusion.

Ten days later, a third infusion of mannitol was attempted. Thirty minutes after the infusion was begun acute pulmonary edema occurred. The mannitol infusion was stopped, usual measures were taken, and the pulmonary edema terminated. Eight hours later another episode of pulmonary edema occurred, did not respond to the usual therapy as had the numerous previous episodes of acute pulmonary edema and the patient died.

The second cardiac patient (case 3) treated with mannitol had coronary artery disease with refractory congestive failure. At rest, he had neither dyspnea nor findings of pulmonary congestion. Marked pitting edema of his lower extremities was present, which could not be mobilized. Table 1 demonstrates very small sodium and water excretions, even with daily Thiomerin. Infusion of 350 Gm. of mannitol with the Thiomerin increased the 24-hour sodium excretion by 350 mEq., increased the urinary output to 8,075 ml., and effected a 9½-pound weight loss. As in case 2, potassium excretion was increased during mannitol-Thiomerin diuresis. Chloride excretion followed as the main ion accompanying sodium and potassium.

During the mannitol infusion, pulmonary congestion and dyspnea occurred. These subsided as the mannitol infusion was slowed or stopped. At the end of the treatment day, all but a trace of the edema of the lower extremities was gone. Since this was the main manifestation of his cardiac decompensation, the

mannitol-Thiomerin treatment was a clinical success in this instance.

Treatment of Cirrhotic Edema. One patient (case 4), with typical Laennec's cirrhosis, marked emaciation, and marked ascites (but without edema elsewhere) that was refractory to diuretic therapy was treated with mannitol plus Thiomerin. Table 1 summarizes the data. Control excretion of sodium was 1.2 mEq. per day. Thiomerin alone increased sodium excretion to 50 mEq. whereas infusion of 475 Gm. of mannitol with Thiomerin increased the sodium loss to 469 mEq. This huge increase in sodium excretion was accompanied by a urinary volume of 8,075 ml., and a weight loss of 17½ pounds. The large urinary losses were derived primarily from mobilized ascitic fluid, since no other edema was present. Potassium excretion was unaffected by mannitol administration. Chloride excretion followed sodium excretion as the accompanying anion. At the end of the infusion, the patient developed muscular rigidity of his extremities and flapping motions of his hands. These disappeared within an hour after the infusion was terminated, and did not recur. Dryness of the mouth and thirst were present throughout the mannitol-Thiomerin treatment day.

Treatment Failures. In 2 patients, one with cirrhotic edema (case 5), and one with nephrotic edema due to lupus erythematosus (case 6), single attempts with mannitol plus Thiomerin did not significantly increase sodium and water outputs, and failed to cause loss of edema fluid. The data are not presented. In both cases, diminished renal function (markedly decreased filtration rates with azotemia) and small doses of mannitol limited the numbers of osmotic diuretic particles reaching the tubular lumens. Thus, these 2 failures may reasonably be attributed to both inadequate dosage and the limiting factor of low filtration rates.

Mechanism of Osmotic Diuresis. Mannitol, in adequate dosage, and in combination with Thiomerin, was a very effective diuretic in cases of refractory edema. In cases 1 to 4, peak urine flows reached were, respectively, 18, 24, 25, and 35 ml. per minute. Study of

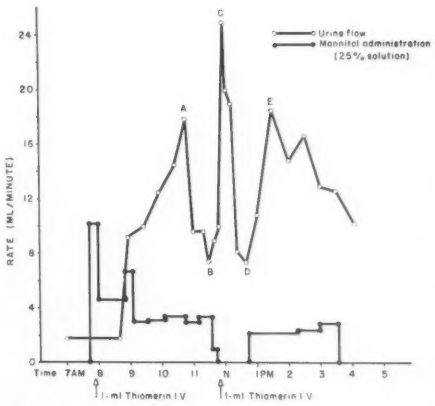


FIG. 2. Case 3, cardiac edema. Rates of urinary flow as related to time of intravenously administered Thiomerin and mannitol.

individual urine specimens revealed that with increasing excretory loads and urine volumes the urine total osmolar concentration (as measured by freezing point depression) decreased asymptomatically toward 310 mOsM. per L.; and the urine specific gravity asymptomatically toward 1.010. These conform to the characteristics of urine under osmotic diuretic circumstances.[1-3]

The much greater natriuretic and diuretic effects of mannitol and Thiomerin combined as compared with either alone are demonstrated by the data in table 1, and are clearly shown by the time course of urinary flow rates in relation to the Thiomerin and mannitol administration in figure 2 (case 3). The first peak excretion rate (*A*) represents the maximal effect of the first Thiomerin injection at a time of constant mannitol infusion. The first nadir (*B*) represents the lessened effect of the first Thiomerin injection with the mannitol infusion unchanged. The second peak (*C*) represents the combined effects of the second Thiomerin injection and high mannitol plasma levels. (The mannitol infusion had been stopped, but significant removal by excretion or utilization of the extracellularly distributed mannitol had not yet occurred. That peripheral utilization of mannitol contributes significantly to fall in plasma mannitol levels is indicated by total recoveries of only 34 and 43 per cent, respectively, of the

TABLE 2.—*Serum Electrolyte Concentrations before and after Mannitol Plus Mercurial Diuretics*

	Day	Treatment day	Serum concentration (mEq./L.)†			
			Na	K	Cl	HCO_3
Case 2	2	—	121	5.8	86	18.6
	3	X	—	—	85	24.2
	7	X	120	4.4	87	19.5
	8	—	121	3.6	—	—
Case 3	−3‡	—	145	5.7	95	—
	−2‡	—	—	4.8	93	35.8
	3	X	—	—	—	—
	6	—	144	4.5	92	35.0
Case 4	−4‡	—	132	3.7	100	28.9
	3	X	—	—	—	—
	4	—	139	3.1	99	25.9

* Treatment with mannitol plus Thiomerin.
† Fasting a.m. levels.
‡ Days before day 1 of table 1.

total doses administered in cases 1 and 4.) The second nadir (*D*) occurred during the effect of the second Thiomerin injection after the plasma mannitol level had become lowered by excretion and utilization following cessation of the mannitol infusion. The third peak (*E*) occurred following the restarting of mannitol infusion while the effect of the second Thiomerin injection was still present. Thus, nadir *B* represents the diuretic effect primarily of mannitol, and nadir *D* represents the effect primarily of Thiomerin; whereas peaks *A*, *C*, and *E* each represent the combined effects of mannitol and Thiomerin.

Discussion

These data demonstrate the effectiveness of an osmotic diuretic combined with a mercurial diuretic in treatment of refractory edema. In 1 nephrotic patient, mannitol with Thiomerin was effective and without adverse reactions. In 2 cardiac patients, as was predicted, the mannitol infusion caused pulmonary edema during the osmotic diuresis. In 1 cirrhotic patient, marked diuresis was followed by early signs of central nervous system symptoms of hepatic insufficiency. In 2 other patients, one with Laennec's cirrhosis, the other with the nephrotic syndrome of lupus erythematosus, diuresis failed to occur because of both inadequate dosage and markedly reduced filtration rates. The effect of mannitol in nonrefractory edema[14] was not studied.

The increased effectiveness of the combination of an osmotic and a mercurial diuretic[5, 8] probably can be explained by their known different actions. Mannitol, by its water-retaining and sodium-diluting action, decreases the numbers of sodium-absorbing sites of the tubular cells that are exposed to sodium;[1] Thiomerin reduces the avidity of each of these decreased numbers of sites for sodium resorption.[5, 6, 15] The combined effects result in great proximal tubular rejection of sodium (and accompanying anions). Both mannitol[2, 3] and nonabsorbed sodium[4] (due to mercurial effects on tubular cells) have been shown to act as osmotic diuretics. The nonabsorbed ions[4] and the mannitol retain water isosmotically in the proximal tubule and thus present excessive amounts of water and electrolytes to the distal tubule which are followed by excess excretion. It would be expected that any osmotic diuretic could be effectively combined with any metabolic diuretic that acted directly on the active cell mechanism for sodium transport. The factors influencing excretion of sodium are so numerous and variable that no absolute values of sodium excretion may be expected for given doses of mercurials, osmotic diuretics, or combinations of diuretics. What is demonstrated is the ability of osmotic diuretics to increase the tubular rejection of sodium from whatever level of rejection existed immediately prior to their use.[4-6, 15-17]

Despite the great losses of water, sodium, and chloride during the course of combined mannitol-Thiomerin treatment (table 1) no clinically significant changes of serum sodium, potassium, chloride, or bicarbonate concentrations occurred, as is demonstrated by values during treatment in case 1 (fig. 1) or before and after treatment in cases 2 to 4 (table 2).

No substantial difference was found between the natriuretic or diuretic effects of

mannitol plus Thiomerin in the patients with refractory edema of renal, cardiac, or hepatic origin. The diuretics were effective in shifting toward greater tubular rejection of sodium and water. The similarity of diuretic effects conforms with the concept that in these different states excessive sodium resorption by tubular cells, due mainly to increased aldosterone effect, is the final common pathway for the development of edema.[18]

The clinical value of osmotic diuretics in refractory edema must be evaluated by more extended studies. The hazards of pulmonary edema in cardiac patients may be minimized by use of adequate doses of urea or other osmotic diuretics that are distributed throughout body water rather than extracellular fluid alone. In cirrhotic patients, the effects of repeated treatment gradually to remove extensive ascites and peripheral edema must be evaluated.

The use of (physical) osmotic diuretics in large adequate doses in combination with (metabolic) tubular cell sodium resorption blocking diuretics should be considered when edema states are refractory to all other diuretic therapy.

Summary

Mannitol, a typical osmotic diuretic, was administered intravenously in large doses (up to 475 Gm. in 8 hours) to a small number of patients with edema refractory to other diuretic therapy. Whatever the previous levels of sodium, chloride, and water excretion, the administration of mannitol markedly increased those levels of excretion.

The combination of mannitol and a mercurial diuretic was much more effective than either alone in increasing excretion of sodium (up to 660 mEq. per day) and water (up to 8,685 ml. per day), and causing weight (edema) losses whether the edema was of renal, cardiac, or hepatic origin. Negligible to very large weight losses occurred, being determined by both excretions and simultaneous intakes. Diuretic responses were not necessarily accompanied by clinical benefits. The excretions were not accompanied by clinically significant alterations in serum electrolyte concentrations.

The data conclusively demonstrate the ability of an osmotic diuretic markedly to increase the urinary excretion of water, sodium, and chloride in cases of refractory edema. The mechanism by which this is accomplished is discussed. The hazard of inducing pulmonary edema by administering osmotic diuretics to cardiac patients is recognized. The clinical value of osmotic diuretics must be determined by additional studies.

Acknowledgment

The authors wish to thank Drs. Smith Freeman and Lyle A. Baker for their contributions to this work, and E. E. Bond, J. X. Wheeler, G. Phillips, and D. Perry for their important technical assistance.

Summario in Interlingua

Mannitol, un typic diuretico osmotic, esseva administrate per via intravenose in grande doses (de usque a 475 g in 8 horas) a un micre numero de patientes con edema que esseva refractori a altere formas de therapia diuretic. Sin reguardo al previe valores del excretion de natrium chloruro, e aqua, le administration de mannitol augmentava ille valores marcatemente.

Le combination de mannitol con un diuretico mercurial esseva multo plus efficace que le un o le altere sol in augmentar le excretion de natrium (usque a 660 mEq per die) e de aqua (usque a 8.685 ml per die) e in causar perdiates de peso (de edema), sin reguardo a si le edema esseva de origine renal, cardiac, o hepatic. Le perditas de peso variava inter negligibile e multo pronunciate e esseva determinate per le factores del excretion e del ingestion contemporanee. Le responsas diuretic non esseva necessarimente accompaniate de beneficios clinic. Le excretiones non esseva accompaniate de clinicamente significative alterationes in le concentrationes del electrolytos seral.

Le datos demonstra conclusivemente le facto que un diuretico osmotic es capace a inducer marcate augmentos del excretion urinari de aqua, natrium, e chloruro in casos de edema refractori. Le mechanismo que resul-

ta in iste effecto es discutite. Le risco de inducer edema pulmonar per le administration de diureticos osmotic a patientes cardiac es recognoscite. Le valor clinic de diureticos osmotic debe esser determinate per studios additional.

REFERENCES

1. Shannon, J. A.: The renal reabsorption and excretion of urea under conditions of extreme diuresis. Am. J. Physiol. **123:** 182, 1938.
2. Rapoport, S., Brodsky, W. A., West, C. D., and Mackler, B.: Urinary flow and excretion of solutes during osmotic diuresis in hydropenic man. Am. J. Physiol. **156:** 433, 1949.
3. —, West, C. D., and Brodsky, W. A.: Excretion of solutes and osmotic work during osmotic diuresis of hydropenic man. The ideal and the proximal and distal tubular work; the biological maximum of work. Am. J. Physiol. **157:** 363, 1949.
4. Brodsky, W. A., and Graubarth, H. N.: Mechanism of mercurial diuresis in hydropenic dogs. Am. J. Physiol. **172:** 67, 1953.
5. Vogl, A.: Diuretic Therapy. Baltimore, The Williams & Wilkins Co., 1953.
6. Smith, H. W.: The Kidney. Structure and Function in Health and Disease. New York, Oxford University Press, 1951.
7. Luetscher, J. A.: A study of the mechanism of nephrotic edema. J. Clin. Invest. **26:** 1189, 1947.
8. Mudge, G. H., Foulks, J., and Gilman, A.: Effect of urea diuresis on renal excretion of electrolytes. Am. J. Physiol. **158:** 218, 1949.
9. Bonsnes, R. W., and Taussky, H. H.: Colorimetric determination of creatinine by the Jaffe reaction. J. Biol. Chem. **158:** 581, 1945.
10. Instruction Manual, Flame Photometer Model 52-C, Perkin-Elmer Corp., Glenbrook, Conn.
11. Hawk, P. B., Oser, B. L., and Summerson, W. H.: Practical Physiological Chemistry. Ed., 12, Philadelphia, Blakiston Co., 1948.
12. Corcoran, A. C., and Page, I. H.: A method for the determination of mannitol in plasma and urine. J. Biol. Chem. **170:** 165, 1947.
13. Instruction Manual, Osmometer Model B, Fiske Associates, Inc., Boston, Mass.
14. Last, J. H., McDonald, G. O., Jones, R. A., and Bond, E. E.: Rates of equilibrium of inulin and mannitol between plasma and interstitial water in edematous states. J. Lab. & Clin. Med. **39:** 62, 1952.
15. Smith, H. W.: Principles of Renal Physiology. New York, Oxford University Press, 1956.
16. Simmons, D. H., Harvey, R. B., and Hoshiko, T.: Effect of sodium intake on sodium loss due to mannitol diuresis. Am. J. Physiol. **178:** 182, 1954.
17. Cizek, L. J., and Holmes, J. H.: Chloride excretion during osmotic diuresis in the dog. Am. J. Physiol. **160:** 536, 1950.
18. Bartter, F. C.: The role of aldosterone in normal homeostasis and in certain disease states. Metabolism **5:** 369, 1956.

It is with the living that medicine has to do. The living man must be studied in health as in disease; to the physician or surgeon the sick or wounded man is as the mineral to the geologist, as the star to the astronomer.—William Stokes His Life and Work (1804-1878) by his son William Stokes. London T. Fisher Unwin, MDCCCXCVIII, p. 162.

Serum Lipids in South African Bantu and White Subjects

B. M. Bloomberg, M.D., F. Lazarus, B.Sc., Irene Mrost, B.A., and Rhoda Schneider, B.Sc.

Normal South African Bantus differ from white Europeans in lipoprotein pattern as well as in total serum cholesterol. Urban Bantus have higher α-lipoprotein cholesterol concentrations and lower β-lipoprotein cholesterols than whites. Young rural Bantus have lower α-lipoprotein cholesterols than young urban Bantus, and both have lower β-lipoprotein cholesterols than old urban Bantus. These differences may be related to standards of living and are thought to be of value in defining the "ideal" levels for both cholesterol fractions.

DURING the course of serum lipid studies in the different racial groups of South Africa, it became apparent that normal Bantu (Negro) subjects differed from white South Africans in lipoprotein pattern as well as in total serum cholesterol levels. The findings reported here confirm previous reports by other South African workers,[1-9] but, in addition, considerably higher α-cholesterols and considerably lower β-cholesterols were found in the urban Bantus than in the whites. Further it has been found that young urban Bantus have higher total cholesterol levels than young rural Bantus and this increase is entirely in the α-lipoprotein fraction, whereas the further increase with age in the urban Bantu is confined to the β-lipoprotein fraction. These differences are statistically significant, despite the wide ranges, and may be of importance in defining the "ideal" values of both α- and β-lipoprotein cholesterols. The results are also briefly considered from the viewpoint of determining the "physiological" value of some of the measures proposed for the prevention or treatment of atherosclerosis and coronary thrombosis.

Material and Methods

The lipid studies are reported in 104 males, and brief comparisons are made with similar data obtained in small groups of Bantu and white females. The male subjects consisted of 38 urban Bantus, 39 rural Bantus, and 27 white men. The rural Bantu group were young individuals from tribes of Southern Africa on their first visit to the Rand Gold Mines; their blood samples were collected within a few days of their arrival in Johannesburg, during a short period of hospital treatment for scabies and other minor skin lesions. The urban Bantus consisted of detribalized subjects and were divided into 3 groups: a group of young men in domestic service in "flats" or apartments, a group of old men who were employed by a public utility transport corporation and who received wages above the usual Bantu level; and a convalescent hospital group who had been admitted to the surgical wards for hernial repairs, hemorrhoidectomies, and fractures. The white men represented a "selected" group in the sense that they had been referred by physicians for various laboratory investigations in the fasting state. The opportunity was taken to study the serum lipids and the results were correlated with the clinical diagnosis. No evidence of organic disease was found in 15 "normal" subjects, and non-vascular organic disease was diagnosed in 12 subjects. The diagnoses made in the latter group were peptic ulcer, senile osteoporosis, ? Addison's disease, bronchitis, gout, chronic lymphatic leukemia, leukoderma, lipomata, mycosis fungoides, duodenal ulcer, and (2 cases of) cholelithiasis.

The serum total lipids were estimated by Kunkel's method,[10] the total cholesterol by Pearson's method,[11] and the lipoprotein fractions and their cholesterol components by paper electrophoresis.[12] The β-lipoprotein fraction included both the dense β-lipoprotein band itself, and the "trail" or post-β or "0" fraction.[13] All estimations were performed on serum from venous blood collected in the early morning after an overnight fast. Fasting specimens were considered essential for comparison of total lipids; in addition there may be diurnal variations in various lipid fractions and exercise may also influence the cholesterol level after meals.[14] The analyses were carried out on the great majority of the specimens on the day of collection. The separated serum was stored at 4 C. when the estimations were delayed more than a few hours. Although storage of serum at 0 to 5 C. for periods up to 28 days is said to produce no alteration of the lipoprotein pattern or con-

From Clinical Laboratories, Medical Centre, Jeppe Street, Johannesburg, South Africa.

TABLE 1.—*Classification of Bantu and White Men According to Serum Total Lipids and Total Cholesterol Values*

Group	Number of subjects	Age		Class 1 Normal total cholesterol, normal total lipids		Class 2 Normal total cholesterol, raised lipids		Class 3 Raised total cholesterol, raised lipids	
		Range	Mean	Number of subjects	%	Number of subjects	%	Number of subjects	%
Bantus	77	—	—	—	—	—	—	—	—
1. Young rural	39*	16–29	19	37	95	1	3	—	—
2. Young urban	6	18–31	25	5	83	1	17	—	—
3. Old urban	22	46–71	55	18	82	4†	18	—	—
4. Convalescent urban	10	41–56	45	9	90	1	10	—	—
Whites	27	—	—	—	—	—	—	—	—
5. "Normal"‡	15	33–63	48	12	80	2	13	1	7
6. Nonvascular organic disease	12	39–73	51	11	92	1	8	—	—

* One case not classified with raised cholesterol, but normal total lipid levels.
† One case of diabetes mellitus, and 1 case of "vascular disease."
‡ No evidence of organic disease.

TABLE 2.—*Serum Total Cholesterol and Lipoprotein Cholesterol Fractions in "Normocholesteremic" Bantu and White Men (Classes 1 and 2)**

Group†	Number of Subjects	Total cholesterol		α-Lipoprotein cholesterol				β-Lipoprotein cholesterol			
		mg. per 100 ml.		mg. per 100 ml.		% Total		mg. per 100 ml.		% Total	
		Range	Mean ± S.D.	Range	Mean ± S.D.	Range	Mean ± S.D.	Range	Mean ± S.D.	Range	Mean ± S.D.
Bantus	74										
1.	38‡	87–238	145±38	3–72	30±15	2–46	21±9	54–200	115±33	54–98	79±9
2.	6	136–211	174±29	38–78	61±19	19–49	36±11	81–162	113±33	51–81	64±11
3.	20§	165–270	215±28	21–115	70±24	9–62	33±12	63–216	145±37	38–91	67±12
4.	10	134–228	180±28	30–70	49±12	15–42	27±8	92–180	131±29	58–85	73±8
Whites	26	—	—	—	—	—	—	—	—	—	—
5.	14‖	169–259	221±26	14–49	35±10	8–21	16±4	149–214	186±21	79–92	84±4
6.	12	175–289	218±36	25–58	36±11	9–26	17±5	137–263	182±38	74–91	83±5

* The detailed statistical analysis has been omitted.
† Groups as in table 1.
‡ One subject (not classified) has been excluded from the analysis.
§ Two subjects, one of whom had diabetes mellitus, and one "vascular disease," have been excluded.
‖ One subject in class 3 has been excluded.

tent,[15] it has been our experience that paper electrophoretograms on serum stored for longer than 24 hours at 4 C. may show a slight decrease in α-lipoprotein and a corresponding increase in β-lipoprotein.

RESULTS

The various groups into which the subjects have been divided are shown in table 1, and each group has been further classified according to the serum total lipid and total cholesterol concentrations. Class 1 includes all the subjects whose total lipids were below 700 mg. per cent and whose cholesterol concentrations were below Keys'[16] upper limit for 90 per cent of an American population of the same ages. These upper limits ranged from 219 mg. per cent at 18 years to a maximum of 332 mg. per cent at 55 years, and thereafter a gradual decrease to 276 mg. per cent at 75 years of age. Cholesterol levels reported for white South Africans[2, 4] and our own unpub-

TABLE 3.—*Serum Total Lipids and Lipoprotein Fractions in "Normocholesteremic" Bantu and White Men (Classes 1 and 2)**

Group†	Number of subjects	Total lipids		α-Lipoprotein		β-Lipoprotein	
		mg. per 100 ml.		% Total lipids		% Total lipids	
		Range	Mean ± S.D.	Range	Mean ± S.D.	Range	Mean ± S.D.
Bantus	74						
1.	38‡	310–780	461±97	0–54	22±13	46–100	78±13
2.	6	480–770	600±34	22–55	36±14	45–78	64±14
3.	20§	490–760	617±75	0–52	26±14	48–100	74±14
4.	10	433–750	567±98	12–32	20±8	68–88	80±8
Whites	26						
5.	14‖	470–980	584±61	7–30	19±8	70–93	81±8
6.	12	473–820	612±90	6–26	18±7	74–94	82±7

* The detailed statistical analysis has been omitted.
† Groups as in table 1.
‡ One subject (not classified) has been excluded from the analysis.
§ Two subjects, one of whom had diabetes mellitus, and one "vascular disease," have been excluded.
‖ One subject in class 3 has been excluded.

lished figures are of the same order. Class 2 includes all subjects whose total lipids were above 700 mg. per cent but whose cholesterol levels were below the same upper limits as class 1. Class 3 includes all subjects showing total lipids above 700 mg. per cent and total cholesterol values above Keys' upper limits.

It will be seen from table 1 that only 2 of the young Bantus and only 4 of the older Bantus fell into class 2, and none into class 3, although 1 individual had a raised serum cholesterol while the total lipid concentrations were normal. The white men showed a similar class distribution. In order to determine whether differences existed in "normocholesteremic" subjects a statistical analysis of the data in classes 1 and 2 was carried out. The results are presented in tables 2 and 3, and the more important conclusions follow.

Total Cholesterol and Lipoprotein Cholesterol Fractions (Table 2). The old urban Bantu group shows similar levels of total cholesterol to the "normal" white group (p=0.5) and to the white group with nonvascular organic disease (p=0.8). This lack of difference is surprising in view of previous reports [2,4] and is probably related to the higher standard of living of the old urban Bantu group in this study. This interpretation is supported by the fact that the convalescent Bantu group, which consisted of individuals in poorer economic circumstances, show significantly lower (p<0.01) total cholesterol levels than both old urban Bantus and white subjects, and similar levels to the young urban Bantus. Considerable differences are, however, apparent in the cholesterol fractions. There is a highly significant decrease (p<0.01) in the mean α-lipoprotein cholesterol percentages and absolute values in both white groups when compared to the old urban Bantus, and also a highly significant increase (p<0.01) in the β-lipoprotein-cholesterol percentages and absolute values. In contrast the 2 white groups show no differences in either the percentages (p=0.6) or the absolute values (p=0.8) of the cholesterol fractions. The fact that these differences cancel out in the total cholesterol detracts considerably from the value of estimating the total cholesterol alone.

As for the young Bantus, both the rural and urban groups show significantly lower (p<0.01) mean total cholesterol concentrations than the old urban Bantus. The young rural group, however, shows both significantly lower (p<0.01) α- and β-cholesterol concentrations, whereas the young urban group has

similar α-cholesterols (p=0.3) but lower β-cholesterol concentrations (p<0.05). It is thus apparent that the rise in total cholesterol with age and improved living conditions in the urban Bantu is due to an increase in the β-fraction, whereas the rise from the young rural to the young urban Bantus is due solely to an increase in the α-fraction (p<0.01). It is noteworthy that there is no absolute increase in the β-cholesterol fraction from the rural to the young urban Bantus, the higher mean β-cholesterol percentage of the young rural men being simply a reflection of the lower α-cholesterol concentration.

The α-cholesterol fraction appears to reach an apparent maximum at 60 to 70 mg. per cent in the urban Bantu groups. The minimum β-cholesterol is found in the young urban or rural Bantu—approximately 110 to 115 mg. per cent. It is suggested below that these levels are optimal and on the basis of these figures it would follow that the "optimal" levels for the total cholesterol should be 170 to 185 mg. per cent, for the α-lipoprotein cholesterol percentage 35 to 38 per cent, and for the β-lipoprotein cholesterol percentage 62 to 65 per cent. It is of significance that the percentage and absolute concentrations of α- and β-lipoproteins published for young adult normal white women,[22] confirmed in our laboratory (unpublished findings), agree with these values. Older white women also show significantly lower α-cholesterol percentages and significantly higher β-cholesterol percentages than the old urban Bantus, and this also holds for the absolute concentrations of the α-cholesterol and β-cholesterol fractions. Similar differences are found between old and young adult white women.

Total Lipids and Lipoprotein Fractions (Table 3). The lower total cholesterol concentrations of the young rural Bantus are paralleled by their significantly lower (p<0.01) total lipid levels compared to both young and old urban Bantus. This again appears to be due mainly to the low α-lipoprotein level in the young rural Bantus, which results in a lower α-lipoprotein percentage, and is reflected in a higher β-lipoprotein percentage. Despite the apparent differences in the percentages of the 2 lipoprotein fractions the β-lipoprotein levels do not differ in young rural and urban Bantus. The young urban Bantus, however, show both a higher mean α-lipoprotein percentage and a lower mean β-lipoprotein percentage than the old urban Bantus although the total lipid levels of the 2 groups are not significantly different (p=0.4). Similar conclusions are reached when the young Bantus are compared with the older convalescent Bantu group. Analysis of the lipid and lipoprotein fractions, therefore, confirm the cholesterol findings but the results are in general of lesser significance in view of the greater scatter of the lipoprotein values. This scatter is thought to be due to the inherently greater error in the estimation of the stained lipoprotein bands as compared to the measurement of the cholesterol fractions.[12]

Discussion

It is now generally accepted in American and western European countries that apparently healthy people do not necessarily represent normality, i.e., freedom from atherosclerosis, since myocardial infarction is endemic in these countries. This also appears to be true for white South Africans, whereas the South African Bantu is not so severely afflicted with atherosclerosis.[3] These features have been correlated with the lower cholesterol levels in the Bantu and more recently[7] with lower S_f 12-20 and S_f 20-100 classes of the β-lipoproteins of the Bantu when compared with the "normal" levels for a sample of the New York City white population. No comparable ultracentrifuge studies have yet been reported for normal white South Africans, but the differences in the low density bands of lipoproteins between the Bantu and American groups are supported in the present investigation by the demonstration of significant differences between the α- and β-lipoprotein cholesterols of the Bantu and South African white subjects.

The implications of the differences in the cholesterol fractions between the Bantu and

white groups may be of considerable significance. It is apparent from what has already been said that the "normal" values for cholesterol in countries where atherosclerosis is endemic may be far above the "ideal" value, which could be defined as the cholesterol level in individuals free of atherosclerotic lesions. This of course assumes the validity of the premise that an etiologic relationship exists between cholesterol concentration and atherosclerosis. The substitution of an ideal value for an indefinable "normal" range has much to commend it. The "ideal" serum cholesterol would in practice simply mean the mean value found in communities where a "successful modern civilization"[17] has not been established, and where presumably there is a low incidence of atherosclerosis, and certainly a low incidence of coronary thrombosis.

It has been claimed[17, 18] that a strong argument can be developed for the contention that the ideal serum cholesterol level for an adult human being is about 150 mg. per cent. Such levels have been found in several primitive communities.[19, 20] In this study the mean cholesterol level of the group of rural young Bantu, 145 ± 38 mg. per cent would appear to support this claim, but an examination of the α- and β-lipoprotein cholesterol levels of young rural and urban Bantus reveals the fact that while no difference exists between the mean levels of β-lipoprotein cholesterol, the former show considerably lower α-lipoprotein cholesterol levels. There is also a lower α-lipoprotein percentage in the rural Bantu, which confirms a previous study in Nigeria.[21] It is possible that the low α-lipoprotein level of the rural Bantu studied here and of the African peasants studied in Nigeria is simply an expression of the poor physical state and low-fat intake of these people. With "improved" development the first striking change seen in the young urbanized Bantu is an increase of the α-fraction, which approximately doubles itself and remains at this level in the older groups. Similar α- and β-cholesterol levels have been found in our laboratory for young healthy white women, and we have come to regard the "ideal" value for the total cholesterol as being in the region of 170 to 180 mg. per cent, rather than in the region of 150 mg. per cent, which is the level found in malnourished primitive communities.

Judged by these criteria, all the normocholesteremic white subjects in this study may be considered abnormal. This conclusion is supported by the high incidence of atherosclerosis, despite apparent good health, of the South African white population.

These findings have prompted us to consider the advisability of determining the "ideal" values for both α- and β-cholesterol separately. This would be a logical attempt to extend into the biological field the established physicochemical differences between the α- and β-lipoprotein cholesterol fractions. As a working hypothesis we have regarded the α-lipoprotein component as being better adapted to the "physiologic" transport of fatty acids than the β-lipoprotein. This view is supported by the higher concentrations of this component in human subjects relatively free of atherosclerosis[22] and in those animal species resistant to experimental atherosclerosis, and also by the association of the heparin-clearing factor with α-lipoprotein,[23] although this finding has been challenged.[24] The evidence indicating the "pathologic" background of high levels of β-lipoprotein cholesterol is also well known. If this hypothesis is valid, it follows that racial groups with a low incidence of atherosclerosis and coronary thrombosis have "ideal" levels of α- and β-lipoprotein cholesterol. We consider that the ideal values for α-lipoprotein cholesterol should be 60 to 70 mg. per cent and for β-lipoprotein cholesterol 110 to 120 mg. per cent. A decrease in the α-level combined with an increase in the β-level would favor the development of pathologic arterial changes. However, the apparent paradox of a low α-level in a population group with a low incidence of atherosclerosis would be easily resolved by reference to the level of the β-lipoprotein cholesterol. Where this is at the "ideal" level, it would implicate some

factor other than arterial disease as responsible for the low α-level. Among impoverished African peasants, such an abnormality in fat transport could be due to poor nutrition, which would adequately explain the very low total cholesterol values, e.g., less than 100 mg. per cent not infrequently encountered in these peoples.

Finally this hypothesis and the concept of "ideal" values for both α- and β-cholesterol may help in assessing the therapeutic significance of some of the measures proposed for the treatment of atherosclerosis. For example, although low-fat diets in atherosclerotic subjects decrease the total cholesterol and total lipid levels, they do not alter the α-lipoprotein cholesterol fractions, which remain obstinately below the "ideal" value. This finding suggests that such treatment has no effect on the metabolic abnormality that may underlie the atherosclerotic process. Estrogens on the other hand have been found to correct the pathologic protein-lipid relationships of survivors of myocardial infarction,[25] producing an increase in the α-lipoprotein component and a decrease in the β-component. It is tempting to correlate this effect of estrogens with the normal lipoprotein pattern of the Bantu, since there is evidence of a different estrogen excretion pattern in these people.[26, 27] While treatment with potent estrogens is for obvious reasons not desirable, therapeutic trials with similar compounds showing poor estrogenic activity should be conducted to assess the power of such compounds to alter the lipoproteins to the ideal pattern.

Summary

Both the rural and urban young Bantu groups show significantly lower total cholesterol concentrations compared to the old urban Bantu. The young rural group, however, shows both significantly lower α- and β-cholesterol, whereas the young urban group has similar α-cholesterol but significantly lower β-cholesterol. The increase of total cholesterol with age in the Bantu is thus almost entirely due to increase in the β-fraction, whereas the increase from the young rural to the young urban subjects is due to a significant increase in the α-fraction. It is noteworthy that there is no increase in the β-cholesterol fraction from the young rural to the young urban Bantu.

The mean cholesterol concentrations of old urban Bantus and whites of comparable ages are similar, but the old Bantus show significantly higher α-cholesterol and significantly lower β-cholesterol than the whites. These 2 differences appear to cancel out in the total cholesterol and this fact detracts considerably from the value of this estimation.

The lower total cholesterol concentrations of the rural Bantu are paralleled by their significantly lower total lipid levels, and again this is due mainly to the low α-lipoprotein concentration. The contrast between the lipoprotein fractions of Bantus and whites is similar to the cholesterol patterns, but the results are of less significance in view of the greater scatter of the lipoprotein results.

The findings reported in this paper have prompted us to consider the advisability of determining the "ideal" values for both α- and β-cholesterol separately. This would be a logical attempt to extend into the biological field the established physicochemical differences between the α- and β-lipoprotein cholesterol fractions. Our results suggest that ideal values for α-lipoprotein cholesterol are 60 to 70 mg. per cent and for β-lipoprotein cholesterol 110 to 120 mg. per cent. A decrease in the α-level combined with an increase in the β-level is considered to favor the development of atherosclerosis.

Acknowledgment

Our thanks are due to the Medical Superintendents and Staffs of the Witwatersrand Native Labour Association and Coronation Hospitals, Dr. N. J. Pretorius, Medical Director of Public Utility Transport Corporation, and our many clinical colleagues in Johannesburg for allowing us access to cases under their care, and for their unfailing courtesy and cooperation during the course of this study.

Summario in Interlingua

Le gruppos de juvene bantus, tanto rural como etiam urban, monstra concentrationes

de cholesterol total significativemente plus basse que le gruppo de bantus urban de etates plus avantiate. Tamen, le juvene gruppo rural monstra valores significativemente plus basse tanto pro cholesterol alpha como etiam pro cholesterol beta, durante que le juvene gruppo urban ha simile valores pro cholesterol alpha sed significativemente plus basse valores pro cholesterol beta. Assi le augmento del cholesterol total occurrente in le bantus con le progresso de lor etate es quasi integremente attribuibile a un augmento del fraction beta, durante que le differentia inter le juvene gruppos rural e urban es attribuibile a significativemente altiate valores del fraction alpha in le gruppo urban. Il merita esser notate que le valores de cholesterol beta non es significativemente plus alte in le juvene bantus urban que in le juvene bantus rural.

Le concentrationes medie de cholesterol in bantus urban de etate plus avantiate es simile a illos in blancos de etate comparabile, sed le bantus de etate plus avantiate monstra significativemente plus alte concentrationes de cholesterol alpha e significativemente plus basse concentrationes de cholesterol beta que le subjectos blanc. Iste 2 differentias se cancella apparentemente in le cholesterol total—un facto que reduce considerabilemente le utilitate de iste estimation.

Le plus basse concentrationes de cholesterol total in le bantus rural es parallel a lor significativemente plus basse nivellos de lipido total, e isto es de novo attribuibile principalmente al basse concentration de lipoproteina alpha. Le differentia inter le fractiones lipoproteinic in bantus e in blancos es simile al differentia in le valores pro cholesterol, sed le resultatos in le caso de lipoproteina es minus significative a causa de un plus extense dispersion del valores.

Le constatationes reportate in le presente studio ha inducite nos a considerar le utilitate de determinar valores "ideal" separatemente pro cholesterol alpha e cholesterol beta. Isto esserea un essayo logic de transferer ab le campo physico-chimic a in le campo biologic le establite differentias inter le fractiones de cholesterol a lipoproteina alpha e beta. Nostre resultatos suggere que valores ideal pro cholesterol a lipoproteina alpha es inter 60 e 70 mg pro cento e pro cholesterol a lipoproteina beta inter 110 e 120 mg pro cento. Un reduction del fraction alpha combinate con un augmento del fraction beta es considerate como un factor favorabile al disveloppamento de atherosclerosis.

REFERENCES

1. Becker, B. J. P.: Cardio-vascular disease in the Bantu and Coloured races of South Africa. IV. Atheromatosis. South African J. M. Sc. **11**: 97, 1946.
2. Walker, A. R. P., and Arvidsson, U. B.: Fat intake, serum cholesterol concentration, and atherosclerosis in the South African Bantu. Part I. Low fat intake and the age trend of serum cholesterol concentration in the South African Bantu. J. Clin. Invest. **33**: 1358, 1954.
3. Higginson, J., and Pepler, W. J.: Fat intake, serum cholesterol concentration, and atherosclerosis in the South African Bantu: II. Atherosclerosis and coronary artery disease. J. Clin. Invest. **33**: 1366, 1954.
4. Bronte-Stewart, B., Keys, A., Brock, J. F., Moodie, A. D., Keys, M. H., and Antonis, A.: Serum-cholesterol, diet and coronary heart-disease. Lancet **2**: 1103, 1955.
5. Bersohn, I., and Wayburne, S.: Serum cholesterol concentration in new-born African and European infants and their mothers. Am. J. Clin. Nutrition **4**: 117, 1956.
6. Bloomberg, B. M.: Serum lipoproteins in relation to atherosclerosis and coronary thrombosis. South African Practit. **1**: 253, 349, 429, 478, 1956.
7. Ruskin, H., Cohn, T. D., Bloomberg, B. M., and Greenblatt, I. J.: Serum betalipoprotein studies in the South African Bantu. Am. J. M. Sc. **235**: 138, 1958.
8. Walker, A. R. P., and Bersohn, I.: Why atherosclerosis? Medicine in South Africa. Supplement to South African M. J., pp. 106-114, 1957.
9. Woods, J. D., and Laurie, W.: Atherosclerosis in the Bantu. Lancet **1**: 1091, 1957.
10. Kunkel, H. G., Ahrens, E. H., and Eisenmenger, W. J.: Application of turbidimetric methods for estimation of gamma globulin and total lipid to the study of patients with liver disease. Gastroenterology **11**: 499, 1948.
11. Pearson, S., Stern, S., and McGavack, T.

H.: A rapid procedure for the determination of serum cholesterol. J. Clin. Endocrinol. & Metab. **12**: 1245, 1952.

12. Bloomberg, B. M., Jankelowitz, R., and Lazarus, F.: A simple paper electrophoresis procedure for the determination of the percentage concentration of serum α- and β-lipoproteins and their cholesterol components. South African J. M. Sc. **20**: 140, 1955.
13. Adlersberg, E., Bossak, E. T., Sher, I. H., and Sobotka, H.: Electrophoresis and monomolecular layer studies with serum lipoproteins. Clin. Chem. **1**: 18, 1955.
14. Keys, A., Anderson, J. T., and Michelsen, O.: Serum cholesterol in men in basal and nonbasal states. Science **123**: 2, 1956.
15. Report of the Technical Group and Committee on Lipoproteins and Atherosclerosis of the National Advisory Heart Council: Evaluation of serum lipoprotein and cholesterol measurements as predictors of clinical complications of atherosclerosis. Report of a cooperative study of lipoproteins and atherosclerosis. Circulation **14**: 691, 1956.
16. Keys, A., Michelsen, O., Miller, E. v. O., Hayes, E. R., and Todd, R. L.: The concentration of cholesterol in the blood serum of normal man and its relation to age. J. Clin. Invest. **29**: 1347, 1950.
17. Leading Article. Serum-cholesterol and myocardial infarction. Lancet **1**: 1286, 1957.
18. Lawry, E. Y., Mann, G. V., Peterson, A., Wysocki, A. P., O'Connell, R., and Stare, F. J.: Cholesterol and beta-lipoproteins in the serums of Americans: Well persons and those with coronary heart disease. Am. J. Med. **22**: 605, 1957.
19. Keys, A., and Anderson, J. T.: The relation of the diet to the development of atherosclerosis in man. *In* Symposium on Atherosclerosis. National Academy of Science. National Research Council Publication No. 338. 1955, pp. 181-197.
20. Toor, M., Katchalsky, A., Agmon, J., Allalouf, D., and Bregman, E.: Serum-lipids and atherosclerosis among Yemenite immigrants in Israel. Lancet **2**: 1270, 1957.
21. Mann, G. V., Nicol, B. M., and Stare, F. J.: The beta-lipoprotein and cholesterol concentration in sera of Nigerians. Brit. M. J. **2**: 1008, 1955.
22. Barr, D. P.: George E. Brown memorial lecture. Some chemical factors in pathogenesis of atherosclerosis. Circulation **8**: 641, 1953.
23. Korn, E. D.: Clearing factor, a heparin-activated lipoprotein lipase: II. Substrate specificity and activation of coconut oil. J. Biol. Chem. **215**: 15, 1955.
24. Robinson, D. S., and French, J. E.: The heparin clearing reaction and fat transport. Quart. J. Exper. Physiol. **42**: 151, 1957.
25. Russ, E. M., Eder, H. A., and Barr, D. P.: Influence of gonadal hormones on protein-lipid relationships in human plasma. Am. J. Med. **19**: 4, 1955.
26. Bersohn, I., and Oelofse, P. J.: A comparison of urinary oestrogen levels in normal male South African Bantu and European subjects. South African M. J. **31**: 1172, 1957.
27. Bloomberg, B. M., Miller, K., Keeley, K. J., and Higginson, J.: Urinary oestrogens and neutral 17-oxosteroids in the South African Bantu with and without hepatic disease. J. Endocrin. In press 1958.

When first I applyed my mind to observation from the many dissections of Living Creatures as they came to hand, that by that means I might find out the use of the motion of the Heart and things conducible in Creatures; I straightwayes found it a thing hard to be attained, and full of difficulty, so with Fracastorius I did almost believe, that the motion of the Heart was known to God alone.—William Harvey. *De Motu Cordis*, 1628.

Venous-Arterial Admixture in the Lungs in Primary and Secondary Polycythemia

By James P. Lillehei, M.D., M.S., Robert L. Johnson, Jr., M.D., Nancy Wu, M.D., E. Richard Halden, M.D., and Brian J. Sproule, M.D., M.S.

By use of a polarographic technic for measuring arterial oxygen tension, venous-arterial shunting in the lungs was investigated in patients with primary and secondary polycythemia before and after treatment and in nonpolycythemic normal and emphysematous subjects.

ALTHOUGH the arterial oxygen saturation is normal in most patients with polycythemia vera,[1, 2] it is sometimes reduced.[3-5] The causes of such reduction are uncertain, but decreased diffusion capacity and damage to the respiratory center are among the possibilities that have been suggested. Most aspects of pulmonary function, however, are not significantly deranged in patients with polycythemia vera.[2] The oxygen dissociation curve is normal.[5] Intrapulmonary venous-arterial admixture was found by Cassels and Morse[5] to be no greater in polycythemic patients than in normal subjects, but the technic they employed for estimating it left much to be desired.

The following report deals with studies of venous-arterial admixture in the lungs of patients with both primary and secondary polycythemia and involves a more sensitive method than that used by Cassels and Morse. For comparison, similar studies were also made in normal subjects and in nonpolycythemic patients with severe chronic bronchopulmonary disease and pulmonary emphysema.

Method

Arterial oxygen saturation was determined by direct sampling with the subject breathing room air.

Venous-arterial admixture was then estimated by determining the alveolar-arterial oxygen gradient after the patient had breathed pure oxygen for 30 or more minutes. Another arterial sample was collected anaerobically, using a syringe that had been heated to body temperature. The syringe was capped, quickly transferred to a heated centrifuge, and centrifuged in a special cup for 90 seconds. An air-tight polarograph cell fitted with a dropping mercury electrode[6] was then filled anaerobically with the supernatant plasma by displacing mercury from the cell, about 1.5 ml. being sufficient for the purpose. An electromotive force of 0.5 volt was applied across the cell and the current produced by reduction of the physically dissolved oxygen at the cathode recorded. The total time from drawing the blood to polarographic recording was 3.5 minutes, the blood and plasma being maintained at 37C. throughout the procedure. Calibration was achieved by equilibrating the patient's plasma in tonometers with 2 or more gas mixtures of known oxygen tension, transferring the plasma anaerobically to the polarograph cell, and determining the oxygen reduction current. From the calibration graph of oxygen tension versus current so constructed, the oxygen tension of any unknown sample can be obtained.

Toward the end of this study an improved method for measuring oxygen tension directly in whole blood was used.[7, 8]

Mean alveolar oxygen tension was calculated from the alveolar equation. Arterial carbon dioxide tension was estimated, using the nomogram of Singer and Hastings[9] by measuring arterial pH and carbon dioxide content. During pure oxygen breathing with complete nitrogen washout, the calculation of mean alveolar oxygen tension becomes:

$$P_{AO_2} = B - P_{H_2O} - P_{aCO_2}$$

where P_{AO_2} = Mean alveolar O_2 tension
B = Barometric pressure
P_{H_2O} = Water vapor tension at 37C. (47 mm. Hg)
P_{aCO_2} = Arterial CO_2 tension (assumed to be same as alveolar CO_2 tension)

From the Cardiopulmonary Laboratory of the Department of Internal Medicine, University of Texas Southwestern Medical School, Dallas, Tex.

This work is part of a project being supported by a grant from the U. S. Public Health Service (H-2113).

TABLE 1.—*Pulmonary Function Studies*

Patient and (age)	Date	Vital capacity (ml.) (and % of predicted)	0.5 sec. EC / V.C. ×100* (%)	Total capacity (ml.)	Res. vol. / T.C. ×100 (%)	I. I. M.†	Pa CO_2 after 30' O_2 (mm. Hg)
Primary polycythemia							
E.P. (57)	4–27–55	2200 (75)	86	3390	44	2.2	47
	8–31–55						43
P.F. (51)	10– 7–55	5250 (130)	61	5800	36	2.3	34
	11– 9–55						43
	3–23–56	5050 (125)	60	6037	28	2.3	46
K.H. (40)	9– 5–56						26
	4–16–57						34
J.H. (52)		4830 (126)	54	7900	39	1.0	35
W.B. (54)		3800 (103)	55				37
N.T. (48)		2500 (86)	68	3812	45	2.3	37
Secondary polycythemia							
R.K. (59)	3– 9–56	2160 (53)	30	5920	49	8.0	72
	3–20–56	2260 (56)	29	7195	55	14.0	63
J.E. (57)	10– 1–55	1400 (38)	23				78
	10–21–55	1700 (46)	29	7170	65	5.4	47
	1–23–56	1200 (32)	17	6435	72	10.8	69
J.C. (55)	11–15–55	2300 (57)	24	5500	69	5.6	51
	1–13–56	2250 (56)	29	5400	68	5.5	60
T.F. (57)		1075 (29)	90				72
W.K. (47)		2400 (57)	22				76
Pulmonary emphysema; nonpolycythemic							
S.F. (41)		2100 (51)	19	5570	75	9.7	63
R.Ho. (56)		2600 (62)	35	6430	60	11.1	54
Z.K. (48)		2700 (71)	24	5200	43	4.8	36
R.H. (72)		1600 (44)	23	4940	76	9.4	81
D.Z. (76)		1700 (57)	19	6120	59	4.8	56
B.S. (81)		1200 (40)	37				45
D.L. (59)		2800 (81)	43	5160	45	2.5	38

* Volume of air expired in first 0.5 second expressed as a per cent of the total vital capacity (normal = >58 per cent).

† I.I.M. = Index intrapulmonary mixing.

The alveolar-arterial oxygen tension gradient was then calculated by subtracting arterial oxygen tension, obtained polarographically, from the calculated mean alveolar oxygen tension.

Red cell mass was measured by the radioactive chromium technic[10] with blood collection at 1 and 3 hours.

Fourteen normal subjects, 7 nonpolycythemic

TABLE 2.—*Alveolar-Arterial Oxygen Tension Gradients in Patients before and after Treatment of Polycythemia*

Patient	Date	Treatment	Oxygen saturation (room air breathing)	Hematocrit	RBC mass. (ml./Kg. of body weight)	($P_A O_2$-$Pa O_2$) Alveolar-arterial gradient during 100% O_2 breathing (mm. Hg)
Primary polycythemia						
E.P.	4/27/55	None	90	71	65.2	367
	8/31/55	Phlebotomy and P^{32}	95.5	46	—	168
	10/ 7/55	None	97	54	39.7	137
P.F.	11/ 9/55	Phlebotomy	—	48.5	—	77
	3/23/56	P^{32}	95.5	47.5	—	27
K.H.	9/ 5/56	None	—	52.5	38.8	329
	4/16/57	None	91	50.6	—	326
J.H.	—	None	93	54	42.8	244
W.B.	—	None	93	62	44.6	106
N.T.	—	None	94	67	58	146
Secondary polycythemia						
R.K.	3/ 9/56	None	79	67	52	403
	3/20/56	Phlebotomy	90	48	32	85
	10/ 1/55	None	86.5	57	41.2	293
J.E.	10/21/55	Phlebotomy	89	46	—	109
	1/23/56	P^{32}	—	51	—	145
J.C.	11/15/55	None	79	62	29.3	169
	1/13/56	Phlebotomy	—	48	—	105
T.F.	—	None	83	62	50.4	195
W.K.	—	None	78.5	50	52.6	230

patients with chronic bronchopulmonary disease and pulmonary emphysema, and 11 patients with polycythemia were studied. Based on clinical evaluation including pulmonary function studies (table 1) and the arterial oxygen saturation during room air breathing (table 2; 90 per cent saturation or above considered normal), there were 6 cases of primary polycythemia and 5 cases of secondary polycythemia.

Both polycythemic and nonpolycythemic patients with chronic pulmonary disease were given vigorous treatment with nebulization and bronchodilators via intermittent positive pressure breathing, postural drainage, and antibiotics as indicated prior to our studies. This was done so that the effects of infection, pooled secretions, etc., could be minimized while polycythemia was under study.

None of the desaturated patients had clinical evidence of intracardiac right-to-left shunts.

RESULTS

As a test of the reliability of the polarographic method used, duplicate analyses of arterial oxygen tension during oxygen breathing were compared in 26 consecutive patients. The mean difference between these duplicates was 2.5 ± 2.0 per cent. For unknown reasons, the polarographic technic using a dropping mercury electrode was not reliable for measuring oxygen tension of less than about 150 mm. Hg in plasma and was not used for measurements in these ranges. Above this level there was a straight line relationship between oxygen concentration in plasma and polarographic current. This relationship was not affected by variations in carbon dioxide tension.

TABLE 3.—*Alveolar-Arterial Oxygen Tension Gradients in Subjects without Polycythemia*

	Alveolar-arterial gradient on 100 per cent O_2 breathing (mm. Hg)	
	Mean	Range
Normal subjects (14 cases)	44.4 ±19	0 to 88
Severe bronchopulmonary disease with pulmonary emphysema (7 cases)	63.6 ±28	37 to 118

Table 2 shows the relatively large alveolar-arterial gradients that were observed in patients with polycythemia. In those cases treated with phlebotomy or P^{32} or both, repeat study 11 days to 5½ months later regularly showed a decrease in gradient toward or to normal. Although the red cell mass in case J. C. was within normal limits, the hematocrit was 62 and there was evidence of venous-arterial admixture, as in patients with true polycythemia.

Table 3 shows the mean and range of alveolar-arterial oxygen tension gradients observed in 14 normal subjects, and in 7 patients with severe chronic bronchopulmonary disease and emphysema during 100 per cent oxygen breathing. None were polycythemic. The mean gradient is higher in the emphysema group than in the normal subjects, but there is considerable overlap and the difference is not significant in this small series.

Figure 1 shows the relationship between hematocrit and the alveolar-arterial oxygen tension gradient in a number of normal subjects and patients with various diseases with and without polycythemia. In order to show the low ranges of this relationship, some anemic patients not otherwise reported in this paper have been included. The correlation coefficient is plus 0.55.

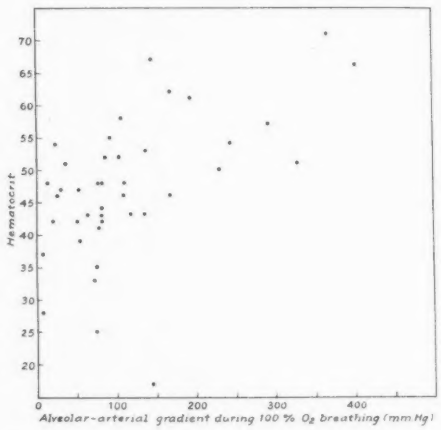


FIG. 1. The relationship between hematocrit and alveolar-arterial oxygen tension gradients.

DISCUSSION

Venous-arterial admixture in the lungs can be identified when the oxygen tension in the arterial blood is significantly less than that of the alveoli. If the subject breathes pure oxygen for 30 minutes before and during these measurements, alveolar nitrogen is virtually eliminated and even the poorly ventilated areas of the lung are highly oxygenated. Likewise, the high oxygen tension brings about almost complete equilibrium between alveolar air and capillary blood, in spite of impaired diffusion. In the absence of an intracardiac shunt, an alveolar-arterial oxygen tension difference that persists under these circumstances must result from shunting of mixed venous blood through lung vessels without adequate exposure to alveolar air.

Our data indicate that the effects of impaired diffusion and of ventilation-perfusion ratio disturbances on the alveolar-arterial oxygen gradient are, in fact, minimized by 30 minutes or more of pure oxygen breathing, because the alveolar-arterial oxygen gradients in a group of nonpolycythemic patients with severe emphysema were normal or only slightly increased. Conversely, the alveolar-arterial gradients were high in untreated primary polycythemia, despite relatively normal pulmonary function.

The possibility that improvement of pulmonary function rather than phlebotomy caused the reduction of alveolar-arterial gradients in patients with secondary polycythemia has been considered. However, there was no consistent relationship between

changes in alveolar-arterial gradient and pulmonary function as measured in our patients. On the other hand, there was invariably an association between reduction of an elevated hematocrit and decrease of the elevated alveolar-arterial gradient.

To the previously recognized benefits of lowering the hematocrit in polycythemia vera can be added the decrease in venous-arterial admixture. However, even the considerable venous-arterial shunting involved accounts for only a small decrease in arterial oxygen saturation during room air breathing. The question of using phlebotomy for treating cor pulmonale with secondary polycythemia remains unsettled.[11, 12] Although the decrease in venous-arterial admixture produced by phlebotomy may raise arterial oxygen somewhat, it is conceivable that a small decrease in blood and tissue oxygen tension might be simultaneously induced by reducing the oxygen capacity of the blood.[13]

At the present time the mechanism of the venous-arterial admixture in association with polycythemia is unknown. The mechanism that appears most worthy of future study is the possibility that normally nonfunctioning shunts between pulmonary artery subdivisions and pulmonary veins become perfused in the presence of polycythemia. Whether these shunts open up as a result of changes in pulmonary blood pressure (perhaps secondary to increased blood viscosity) or blood volume, a combination of both, or by some other mechanism, remains to be elucidated.

Summary

An increased alveolar-arterial oxygen pressure gradient during oxygen breathing has been observed in association with an elevated hematocrit level in patients with either primary or secondary polycythemia. These increased alveolar-arterial oxygen gradients were always decreased toward or to normal when the elevated hematocrit was reduced by phlebotomy or P^{32}.

In a group of nonpolycythemic patients with emphysema the alveolar-arterial gradients during 100 per cent oxygen breathing were near normal. This indicates that the effect of impaired diffusion or ventilation-perfusion disturbances on the alveolar-arterial gradient is virtually eliminated by pure oxygen breathing. The considerable venous-arterial admixture noted in polycythemic patients under the same experimental conditions must be due to anatomic shunting in the lungs.

The fact that the alveolar-arterial gradient can be decreased by reducing the hematocrit level suggests that some sort of cause and effect relationship between the two may exist. The nature of this relationship remains to be elucidated.

Summario in Interlingua

Un augmentate gradiente alveolo-arterial del pression oxygenic esseva observate in association con un elevate nivello hematocritic in patientes con polycythemia primari o secundari durante le respiration de oxygeno. Quando le nivello del hematocrite esseva reducite per phlebotomia o per P^{32}, le gradiente alveolo-arterial de pression oxygenic redescendeva in omne casos verso le norma o mesmo attingeva lo.

In un gruppo de patientes non-polycythemic con emphysema, le gradientes alveolo-arterial esseva in le vicinitate del norma durante le respiration de 100 pro cento de oxygeno. Isto indica que le effecto exercite per defectos de diffusion o de ventilation e perfusion super le gradiente alveolo-arterial es virtualmente eliminate per le respiration de oxygeno pur. Le grado considerabile de mixtura veno-arterial notate in patientes polycythemic sub le mesme conditiones experimental debe resultar de shunts anatomic in le pulmones.

Le facto que le gradiente alveolo-arterial pote esser reducite per abassar le nivello del hematocrite suggere que un relation de causa e effecto existe inter le duo. Le character de iste relation remane a elucidar.

REFERENCES

1. Lawrence, J. H., Berlin, N. I., and Huff, R. L.: The nature and treatment of polycythemia. Medicine **32**: 323, 1953.

2. Ratto, O., Briscoe, W. A., Morton, J. W., and Comroe, J. H., Jr.: Anoxemia secondary to polycythemia and polycythemia secondary to anoxemia. Am. J. Med. **19**: 958, 1955.
3. Harrop, G. A., Jr., and Heath, E. H.: Pulmonary gas diffusion in polycythemia vera. J. Clin. Invest. **4**: 53, 1927.
4. Newman, W., Feltman, J. A., and Devlin, B.: Pulmonary function studies in polycythemia vera. Am. J. Med. **11**: 706, 1951.
5. Cassels, D. E., and Morse, M.: The arterial blood gases, the oxygen dissociation curve, and the acid-base balance in polycythemia vera. J. Clin. Invest. **32**: 52, 1953.
6. Beecher, H. K., Follansbee, R., Murphy, A. J., and Craig, F. N.: Determination of the oxygen content of small quantities of body fluids by polarographic analysis. J. Biol. Chem. **146**: 197, 1942.
7. Clark, L. C., Jr.: Monitor and control of blood and tissue oxygen tensions. Tr. Am. Society for Artificial Internal Organs **2**: 41, 1956.
8. Sproule, B. J., Miller, W. F., Cushing, I. E., and Chapman, C. B.: An improved polarographic method for measuring oxygen tension in whole blood. J. Appl. Physiol. **11**: 365, 1957.
9. Singer, R. B., and Hastings, A. B.: An improved clinical method for the estimation of disturbances of the acid-base balance of human blood. Medicine **27**: 223, 1948.
10. Sterling, K., and Gray, S. J.: Determination of the circulating red cell volume in man by radioactive chromium. J. Clin. Invest. **29**: 1614, 1950.
11. Hecht, H. H., Gaylor, W., and Stein, D.: Vascular adjustments after phlebotomy in polycythemic subjects. J. Clin. Invest. **34**: 939, 1955.
12. Auchincloss, J. H., Jr., and Duggan, J. J.: Effects of venesection on pulmonary and cardiac function in patients with chronic pulmonary emphysema and secondary polycythemia. Am. J. Med. **22**: 74, 1957.
13. Husson, G., and Otis, A. B.: Adaptive value of respiratory adjustments to shunt hypoxia and to altitude hypoxia. J. Clin. Invest. **36**: 270, 1957.

Kuo, P. T., Schnabel, T. G., Jr., Blakemore, W. S., and Whereat, A. F.: Diastolic Gallop Sounds, the Mechanism of Production. J. Clin. Invest. **36**: 1035 (July), 1957.

In these experiments a venous reflux wave was not demonstrated in left or right atrial pressure pulses at the time of the gallop sound. On this basis it is probable that the upward deflection in the jugular venous pulse that follows the V wave depends upon some components of the arterial pulse that are unavoidably included in the venous pulse. Atrial pressure is uniformly higher than that of the ventricle at the time of the gallop. It is concluded that sudden impact or stretching of the ventricle is a better explanation for the genesis of gallop sounds.

Oppenheimer

Serum Lipid and Estrogenic Effects of Manvene, a New Estrogen Analog

Comparison with Premarin in Men with Coronary Heart Disease

By WILLIAM D. COHEN, PH.D., NORIO HIGANO, M.D., AND ROGER W. ROBINSON, M.D.

Estrogenic side-effects and serum lipid changes were studied in middle-aged men with coronary heart disease during a 6-month period with varying dosage levels of Manvene, a new estrogen analog. Although significant lipid-shifting effects were noted at 5 and 10 mg. daily, these were not comparable with those of 10 mg. of Premarin. Analysis of scattergrams of individual estrogenic and lipoprotein responses of both Manvene-treated and Premarin-treated patients revealed a favorable dissociation of these effects in 5 of the 29 men in the Manvene groups.

THE profound changes in the serum lipids resulting from estrogen administration to men and women with coronary heart disease have been documented in several laboratories.[1-6] But these presumably "favorable" alterations have been offset by undesirable estrogenic side-effects, especially in middle-aged men.[3,4] Among many measures suggested to avoid the side-effects, including very low estrogen dosages,[7] intermittent estrogen administration,[8] and various androgen plus estrogen combinations,[9] the most promising appeared to be the use of synthetic analogs of steroidal and nonsteroidal estrogens, which might retain significant lipid-shifting potency and yet lack estrogenicity. Among many estrogen analogs synthesized in the laboratories of G. D. Searle & Co. one, 3-methoxy-16α-methyl-1, 3, 5(10)-estratriene-16β, 17β-diol (Manvene), showed lipid-shifting effects in the rabbit and the chick, anti-atherogenic effects in the chick, but only slight estrogenic activity when tested in mouse uterine growth or rat vaginal smear assays.[10] The results of subacute and chronic toxicity studies in the rat showed this compound to be devoid of serious toxic side-effects,[10] thus allowing its use in clinical trials.

Such a trial was designed to test whether this dissociation remained valid in men on long-term therapy. Previously reported data for relatively brief treatment periods suggested such a dissociation.[11] The outcome of a 6-month period of therapy with oral Manvene at 3 dosage levels is the basis of this report.

MATERIAL AND METHODS

Clinical Material. Forty-nine middle-aged ambulatory men, who had recovered from proved myocardial infarction, were selected for study. These patients were seen in private practice and were largely business, professional and white-collar workers, 60 per cent of whom were of Northern European or Anglo-Saxon descent.

Clinical evaluations were done prior to therapy, together with at least 2 complete serum lipid studies. Twenty-nine patients were divided into 3 groups and placed on 2.5, 5.0, or 10.0 mg. of Manvene daily for 6 months, with monthly clinical and serum lipid studies. For comparison, 20 patients were placed on 10 mg. daily of oral, mixed conjugated equine estrogens, N.N.R. (Premarin) on a long-term basis, and were re-evaluated at 1, 2, and 6 months of therapy. The structural formulas of Manvene and sodium estrone sulfate, the chief constituent of Premarin, are shown in figure 1.

Estrogenic side-effects in both the Premarin and Manvene groups were graded according to the schema of table 1.

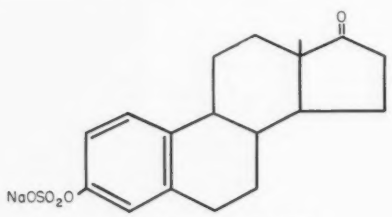
From The Medical Division and The Research Laboratory, The Memorial Hospital, Worcester, Mass.

This work was supported by grants from G. D. Searle and Co. and the Worcester District Chapter, Massachusetts Heart Association.

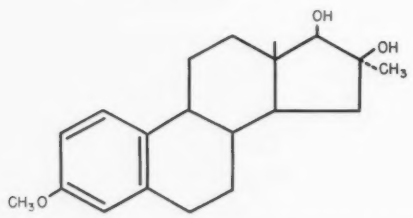
A preliminary report was presented at the Tenth Annual Meeting of the American Society for the Study of Arteriosclerosis, Chicago, Ill., Nov. 12, 1956.

TABLE 1.—*Scoring of Estrogenic Side-effects*

Side Effects	2 Months	6 Months
Breast tenderness		
Slight	1	1
Moderate to severe	2	2
Breast hypertrophy		
Slight	2	2
Moderate to severe	4	4
Depression of sex functions		
Slight to moderate	1	1
Complete	2	2
Maximum possible score	8	8
Total		16



SODIUM ESTRONE SULFATE

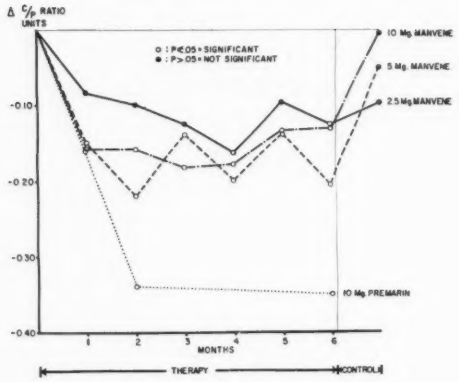


3-METHOXY-16α-METHYL-1,3,5(10)-ESTRATRIENE-16β,17β-DIOL [MANVENE®]

FIG. 1. Structures of Manvene and sodium estrone sulfate, the principal active estrogen of Premarin.

The reason for the assignment of more weight to breast hypertrophy than to the other categories is the objectivity of this effect, ruling out any misinterpretation due to the bias of either the examiner or the patient.

Biochemical Methods. Total serum cholesterol and lipid phosphorus were determined by the standard methods of this laboratory;[4] phospholipids and cholesterol/phospholipid (C/P) ratios were calculated in the conventional way. Ultracentrifugal separation of the α- and β-lipoproteins, determination of the cholesterol content of the 2 fractions, and calculation of the β-/α-lipoprotein cholesterol ratios were done as described in an earlier communication.[5]



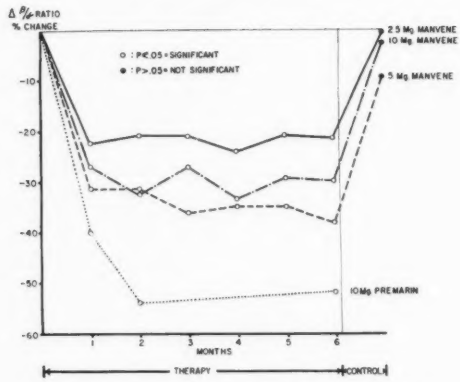


FIG. 2 *Top.* Changes in C/P ratio during 6 months of therapy with Premarin or with various dosages of Manvene.

FIG. 3 *Bottom.* Percentage changes in β-/α-lipoprotein cholesterol ratios during 6 months of therapy with Premarin or with various dosages of Manvene.

RESULTS

The average changes of the C/P ratios in the 4 treatment groups are shown in figure 2. At 1 month of therapy, both 5 and 10 mg. dosage levels of Manvene and 10 mg. of Premarin had shown similar lowering effects on the C/P ratio. But from the second month the Premarin group showed a sustained decrease, nearly double that of the 5- and 10-mg. Manvene groups. There was a smaller decrease in the 2.5-mg. Manvene group, reaching statistical significance ($p \leq .05$) only at 4 and 6 months. Post-treatment control studies in the Manvene groups showed

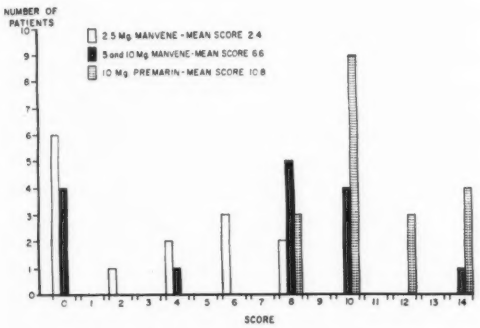


FIG. 4. Side-effects scores of patients treated with Premarin or various dosages of Manvene. Scores are sums of side-effects noted at 2 and 6 months of therapy.

a return to approximate pretreatment levels. Off-treatment data are not available for the Premarin group because therapy was continued beyond the 6-month period of observation.

Similar changes were seen in the β-/α-lipoprotein cholesterol ratios during treatment (fig. 3). Again, the Premarin-treated group showed a greater average response than did the Manvene-treated groups, even at 1 month. Maximum sustained response was attained by 2 months of therapy. This was least in the 2.5-mg. Manvene group. All changes were statistically significant ($p < .01$). Pretreatment levels were attained within 1 month when Manvene therapy was discontinued.

The graded side-effects, derived according to table 1, are shown in figure 4 for all groups. Since both the extent of side-effects and the degree of serum lipid changes were closely akin in the 5- and 10-mg. Manvene groups, these were combined. The mean side-effects score of the Premarin group was 10.8, range 8-14. The mean score of the 2.5-mg. Manvene group was 2.4, and that of the 5- and 10-mg. group, 6.6. Ten of these 29 subjects suffered no side-effects. Analysis of the individual responses to Manvene was carried out by constructing a scattergram to determine whether this substance is in fact a nonestrogenic lipid-shifting agent.

In the upper portion of figure 5 the individual responses of the Premarin group are

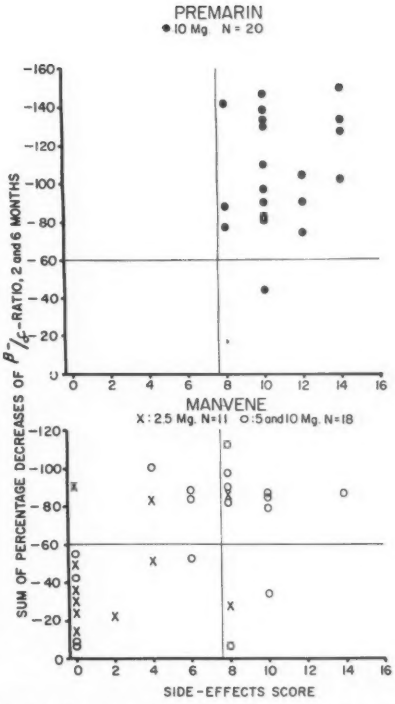

PREMARIN
● 10 Mg. N = 20
SUM OF PERCENTAGE DECREASES OF β-/α-RATIO, 2 and 6 MONTHS
MANVENE
X: 2.5 Mg. N=11 O: 5 and 10 Mg. N=18
SIDE-EFFECTS SCORE

FIG. 5. Scattergrams comparing individual lipid-shifting and estrogenic side-effects of Premarin and Manvene.

shown in a scattergram; the sum of the percentage decreases of the β-/α-lipoprotein cholesterol ratios at 2 and 6 months of therapy was used as a measure of lipid-shifting effect and was plotted against the sum of the estrogenic side-effects scores evaluated at the same time. In all but 1 patient, there was excellent serum lipid response, accompanied by significant side-effects.

The corresponding scattergram of the Manvene-treated groups is shown in the lower portion of figure 5. In contrast to the Premarin group, only 9 Manvene-treated patients showed both extensive serum lipid changes and severe side-effects. Twelve patients had no or slight side-effects accompanied by minimal serum lipid changes. There were 8 patients showing a dissociation, 5 of whom were considered to be favorable because of significant serum lipid response with slight side-effects.

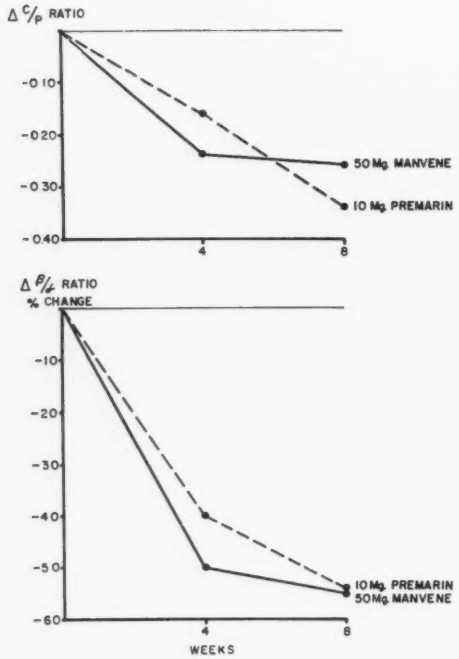


FIG. 6. Comparison of lipid-shifting effects of 10 mg. of Premarin and 50 mg. of Manvene administered daily for 8 weeks.

Nausea was absent in the Premarin group; only 1 patient in the Manvene groups reported this complication. During the 6-month period of observation no patients in either the Premarin or Manvene groups suffered migraine or nocturnal cramps of leg muscles. One patient developed sodium and water retention followed by pulmonary congestion after 2 months of Premarin. Omission of the drug resulted in his recovery.

DISCUSSION

Manvene is clearly a potent lipid-shifting agent in dosages above 2.5 mg. daily. This is shown in its effects on both the C/P and the β-/α-lipoprotein cholesterol ratios. But even at 10 mg., the effects are not as dramatic as those of an equal dosage of Premarin. Analysis of data from a preliminary study of higher Manvene dosages[11] showed that 50 mg. of this drug produced serum lipid changes very similar to those obtained with 10 mg. of Premarin (fig. 6). This Premarin/Manvene "potency ratio" of 5 is similar to that of estrone/Manvene in terms of the C/P ratio lowering effect in cholesterol-fed chicks, also found to be about 5.[10]

Comparative studies of different estrogens using the immature mouse uterus test revealed that Manvene had only 0.3 to 3 per cent of the estrogenic activity of Premarin.[10] This relative lack of estrogenicity has not been borne out by the results in men, since the side-effects scores of patients on 5 or 10 mg. of Manvene daily were often similar to those of the 10-mg. Premarin group. The high incidence of estrogenic side-effects in the 50-mg. Manvene group prevented the continuation of this dosage beyond 2 months. Furthermore, when 10 mg. of Manvene daily were given to 10 postmenopausal women for 7 days, comparison of pretreatment and post-treatment Papanicolaou smears showed uniform cornification of the vaginal epithelial cells, indicating an estrogenic effect. A typical sequence is illustrated in figure 7.

The conventional biologic tests for estrogenic activity have failed to predict the estrogenic potency ratio of Premarin/Manvene in men. It is suggested that the response of the vaginal epithelium of healthy postmenopausal women might be used for the crude estimation of estrogenicity of new lipid-shifting compounds related to the steroidal estrogens before these substances are administered to men. A similar lack of correspondence between estrogenic potency in human beings and in experimental animals has been reported by Brown and Bradbury.[12]

Analysis of the scattergrams of the individual results offers an explanation for the initial impression that Manvene was a practical "weak" estrogen. The similarity of results in 9 Manvene-treated subjects to those seen in the Premarin group implies that these subjects handled Manvene metabolically as another estrogen. In contrast, the 12 men with both minimal lipid changes and side-effects were probably unable to utilize this compound as an estrogen. The favorable dissociation, i.e., significant serum lipid changes and minimal estrogenic side-effects, seen in

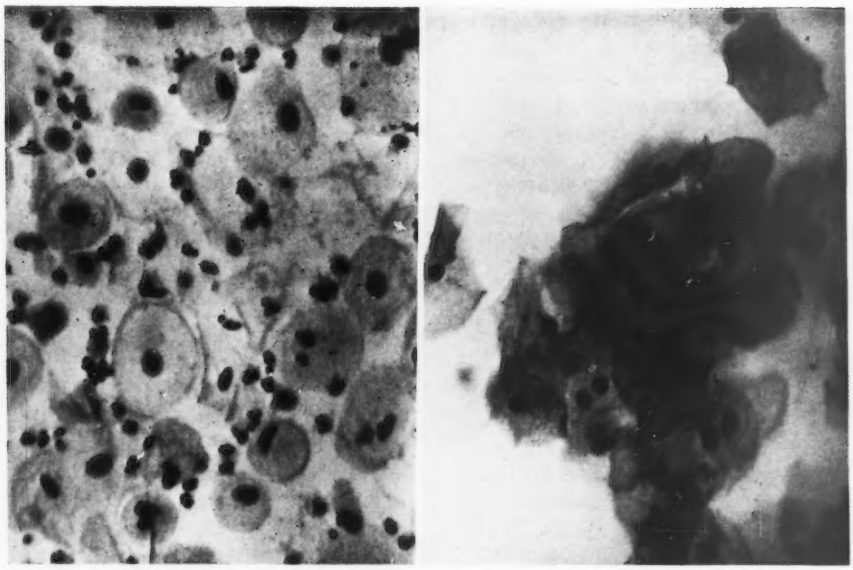


FIG. 7. Vaginal smears of a postmenopausal subject (Papanicolaou stain) (*Left*) before administration of Manvene showing numerous basophilic epithelial cells without cornification, and (*right*) after 10 mg. of Manvene daily for 7 days, showing large polyhedral, cornified epithelial cells, typical of estrogen stimulation.

5 Manvene-treated patients, is encouraging. Thus, a continuing search for other compounds related to both natural and synthetic estrogens is worthwhile, in an attempt to find a substance that uniformly produces a favorable separation of lipid-shifting and estrogenic effects.

SUMMARY AND CONCLUSIONS

A long-term clinical trial of varying dosages of Manvene, a new estrogen analogue, was undertaken to evaluate its usefulness as a lipid-shifting agent without significant estrogenicity in men with coronary heart disease. Similar patients were treated with Premarin, a conventional potent estrogen, for comparison. Serum lipid studies and clinical evaluations were done on all patients during a pretreatment control period and after 2 and 6 months of therapy.

At dosages above 2.5 mg. daily, Manvene produced significant serum lipid changes, lowering both the C/P and β-/α-lipoprotein cholesterol ratios. However, 50 mg. of Manvene were required to match the lipid changes produced by 10 mg. of Premarin.

Manvene produced changes similar to those of adequate doses of conventional estrogens in some subjects, while in others these changes were slight. However, significant serum lipid changes with minimal estrogenic side-effects were seen in 5 of the 29 patients. This observation suggests the feasibility of continuing the search for a truly "nonestrogenic" estrogen derivative with maintained lipid-metabolic effects.

ACKNOWLEDGMENT

We acknowledge with thanks the competent technical assistance of Katherine S. Marsella, Patricia M. LaBranche, and Anne E. Murphy. The Premarin was supplied by Ayerst, McKenna, and Harrison, Ltd., and Manvene by G. D. Searle & Co.

SUMMARIO IN INTERLINGUA

Esseva interprendite un studio clinic a longe vista in le uso de Manvene que es un nove analogo de estrogeno. Le droga esseva administrate in varie doses, e le objectivo del

studio esseva evalutar le utilitate de Manvene como agente capace a modificar le stato lipidic sin producer grados significative de estrogenicitate in masculos con morbo cardiac coronari. Pro objectivos de comparation, un gruppo de patientes simile a illes tractate con Manvene esseva subjicite a un curso de Premarina que es un potente estrogeno conventional. Studios del lipidos seral e evaluationes clinic esseva effectuate pro omne le patientes durante un periodo de controlo ante le tractamento e post 2 e 6 menses de medication.

A dosages supra 2,5 mg per die, Manvene produceva significative alterationes del lipidos seral, abassante tanto le proportion C/P como etiam le proportion lipoproteinic beta/alpha. Tamen, 50 mg de Manvene esseva requirite pro attinger le alterationes lipidic producite per 10 mg de Premarina.

In certe subjectos Manvene produceva alterationes simile a illos producite per adequate doses de estrogenos conventional, sed in altere subjectos le effectos de Manvene esseva leve. Tamen, significative alterationes del lipidos seral con minimal effectos lateral estrogenic esseva observate in 5 del 29 patientes. Iste constatation justifica le continuation del cerca de un vermente "non-estrogenic" derivato de estrogeno in que le effectos super le metabolismo lipidic remane intacte.

REFERENCES

1. Barr, D. P.: Some chemical factors in the pathogenesis of atherosclerosis. Circulation **8**: 641, 1953.
2. Oliver, M. F., and Boyd, G. S.: The influence of the sex hormones on the circulating lipids and lipoproteins in coronary sclerosis. Circulation **13**: 82, 1956.
3. Steiner, A., Payson, H., and Kendall, F. E.: Effect of estrogenic hormone on serum lipids in patients with coronary arteriosclerosis. Circulation **11**: 784, 1956.
4. Robinson, R. W., Higano, N., Cohen, W. D., Sniffen, R. C., and Sherer, J. W., Jr.: Effects of estrogen therapy on hormonal functions and serum lipids in men with coronary atherosclerosis. Circulation **14**: 365, 1956.
5. —, —, and —: The effects of estrogens on serum lipids in women. Arch. Int. Med. **100**: 739, 1957.
6. —, Cohen, W. D., and Higano, N.: Estrogen replacement therapy in women with coronary atherosclerosis. Ann. Int. Med. **48**: 95, 1958.
7. Oliver, M. F., and Boyd, G. S.: Endocrine aspects of coronary sclerosis. Lancet **271 (2)**: 1273, 1956.
8. Adlersberg, D.: Hormonal influences on the serum lipids. Am. J. Med. **23**: 769, 1957.
9. Russ, E. M., Eder, H. A., and Barr, D. P.: Influence of gonadal hormones on protein-lipid relationships in human plasma. Am. J. Med. **19**: 4, 1955.
10. Cook, D. L., and Edgren, R. A.: SC-6924: Pharmacological studies. Personal communication from Division of Biological Research, G. D. Searle & Co., Chicago, Ill.
11. Robinson, R. W., Cohen, W. D., and Higano, N.: Serum lipid and estrogenic effects of two "weak estrogens" in male patients with coronary atherosclerosis. Abstracted, Circulation **14**: 489, 1956.
12. Brown, W. E., and Bradbury, J. T.: The use of the human vaginal smear in the assay of estrogens. J. Clin. Endocrinol. **9**: 725, 1949.

At the outset I would like to emphasize the fact that the student of internal medicine cannot be a specialist. The manifestations of almost any one of the important diseases in the course of a few years will 'box the compass' of the specialities.—William Osler, M.D. *Internal Medicine as a Vocation.* Med. News (N.Y.), 1897.

An Evaluation of Blood Nitrate Levels

By JOHN W. BERRY, M.D., THOMAS C. ROACH, M.D.

The lack of a suitable objective yardstick to measure the effect of anti-anginal drugs has led to confusion in their clinical evaluation. A method of quantitating the nitrate level in the serum has furnished a means of correlating the subjective relief with this group of drugs. Representative samplings of serum from noncardiac and cardiac patients were analyzed to establish control nitrate levels. The cardiac patients were selected for their good responses to nitroglycerin and pentaerythritol tetranitrate. A good subjective response to the drugs correlated with the increased blood nitrate levels.

THE difficulties inherent in evaluating anti-anginal drugs have been stressed by a number of authors.[1-3] In general the lack of an objective yardstick for determining a subjective response remains the problem. It has been noted that favorable reports of a variety of drugs when subjected to the double blind technic of administration fail to bear out the initial enthusiasm.[4] On the other hand, carefully controlled clinical studies have indicated that at least one drug—pentaerythritol tetranitrate (PETN)—is helpful in the chronic management of anginal patients.[7, 11, 16] In an attempt to resolve some of the discrepancies alluded to, a study was undertaken to measure blood nitrate levels in a group of patients. The development of a quantitative method for the microanalysis of blood nitrates is the basis for this report.[9] It was felt that differences in individual absorptions of the nitrate radical might explain the variable clinical findings in the evaluation of these drugs. Glyceryl trinitrate (nitroglycerin) and pentaerythritol tetranitrate (PETN) were chosen for the study. The latter drug was evaluated in 2 dosage forms—tablets and in a timed disintegration capsule (PETN-TD) shown to have a more prolonged and even release of the medicament.[8-13]

METHOD

Selected patients from the medical wards and the outpatient clinic of the St. Louis City Hospital were utilized for these studies. The patients were divided into 2 groupings: a "control" group and a "cardiac" group. The control group of patients had been hospitalized for reasons other than coronary artery disease. All were recovering from their illnesses and were in good clinical condition at the time of the studies. None of the control patients had received any nitrate drugs during his illness. The cardiac group consisted of selected patients from the Cardiac Out Patient Clinic on whom the diagnosis of angina pectoris had been made by the usual clinical history of chest pain brought on by exertion. All of the selected cardiac patients had experienced relief within 10 minutes of the acute attacks of angina pectoris with sublingual nitroglycerin. All of the selected cardiac patients had been maintained on PETN tablets in varying doses of 40 to 80 mg. per day for 1 to 3 months with good control of the anginal attacks. A patient was considered to have good control when there had been a 75 per cent reduction in the number of daily angina attacks from the pre-nitroglycerin control period. A deliberate effort was made to exclude from the cardiac group angina pectoris that might be associated with factors other than coronary artery disease. This was accomplished by excluding by the appropriate clinical methods all patients with valvular heart disease, myocardial infarction, and cardiomegaly greater than 25 per cent of the expected norm, and who did not have the expected subjective response to nitroglycerin. It is emphasized that the "cardiac" group of patients was selected by the typical therapeutic response to nitroglycerin and to PETN administered chronically. The selected anginal patients were ambulatory throughout the study period and hospitalized only for 24 hours to obtain the blood sampling for the nitrate determinations.

From each of the 2 groups of patients under specified conditions, whole blood was collected for nitrate determinations. The collected blood was centrifuged and the sera stored in a commercial type deep freeze at —4 C. until used. The analysis for serum nitrates was done by a modification of the Yogoda method, on a Beckman spectrophotometer with readings at 408 μ.[9, 10]

From the Department of Internal Medicine, St. Louis University School of Medicine and The St. Louis City Hospital, St. Louis, Mo.

TABLE 1.—*Normal Limits of Serum Nitrate*

Subject	Determination 1	Determination 2
A (Grey)	4.0	4.5
B (White)	5.2	5.0
C (Young)	4.0	4.2
D (Schaeffer)	5.0	4.8
E (Hazeltine)	5.7	5.6
	Ave. 4.8	Ave. 4.8

Range 4.0 to 5.7 μg. per ml.

RESULTS

From the *control* patients the normal limits for serum nitrates were determined. This was accomplished by obtaining fasting blood specimens on 5 different subjects. Table 1 shows the results of these studies. The normal range of blood nitrates by the methods used was 4.0 to 5.7 μg. per ml. of serum. To check the reproducibility of our technics, determinations on the stored sera were run another time. Of the paired determinations on the sera, little variation is noted; the greatest difference being 0.5 μg. per ml. of serum. The effect of diet upon the blood nitrate levels was determined on the blood specimens from 5 other control patients. The patients all received the regular hospital diet and were ambulatory on the ward. Blood was obtained, on each patient, at 2-hour intervals during the day. The serum nitrate level subsequently was determined for each patient. Figure 1 shows the average nitrate determinations on the sera of the 5 control patients for the 12-hour observation period. It is evident that a slight diurnal pattern is present with the highest peak in the late afternoon.

The effect of nitrate drugs with an antianginal action upon the nitrate blood levels of control patients was determined. Figure 2 graphically shows the effect of nitroglycerin. In this experiment, 3 control patients were given 0.0012 Gm. (1/50 gr.) of nitroglycerin sublingually. Blood samples were drawn at 2, 4, 6, 10, 12, and 15 minutes following the medication. The average serum nitrate levels for the 3 patients are shown in figure 2. The peak level was reached at 6 minutes, with dissipation by 15 minutes. The

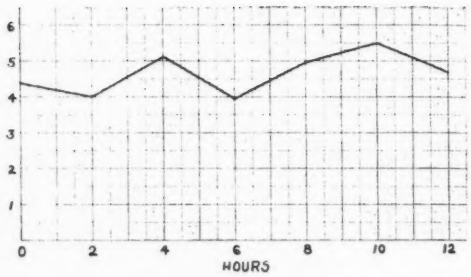


FIG. 1. Controls. No medication, 5 cases, duplicated. *Ordinate*, μg. NO_3 per ml. serum.

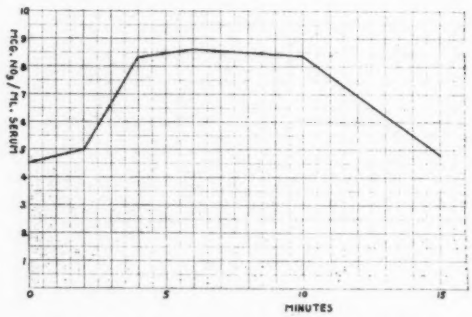


FIG. 2. Nitroglycerin 1/50 gr., 3 cases.

figures obtained are consistent with the fairly rapid action of nitroglycerin for the acute treatment of angina pectoris. It is of interest that the blood nitrate levels lag behind the expected time for clinical relief of the anginal pain.[14]

The results of PETN on the blood nitrate levels of the control group of patients were obtained. For this experiment, 6 patients were selected and divided into 3 groups of 2 each. Each pair of patients were given respectively an identically colored capsule containing a placebo of lactose, 30 mg. PETN plain capsules, and 30 mg. PETN timed-disintegrating capsules. The capsules were given to each pair of patients at 12-hour intervals for 3 days. The capsules were distributed by one of us without prior knowledge of their content. The contents of the capsules were subsequently made known after the laboratory data had been completed. At the conclusion of the third day of treatment, blood samples from each pair of patients were

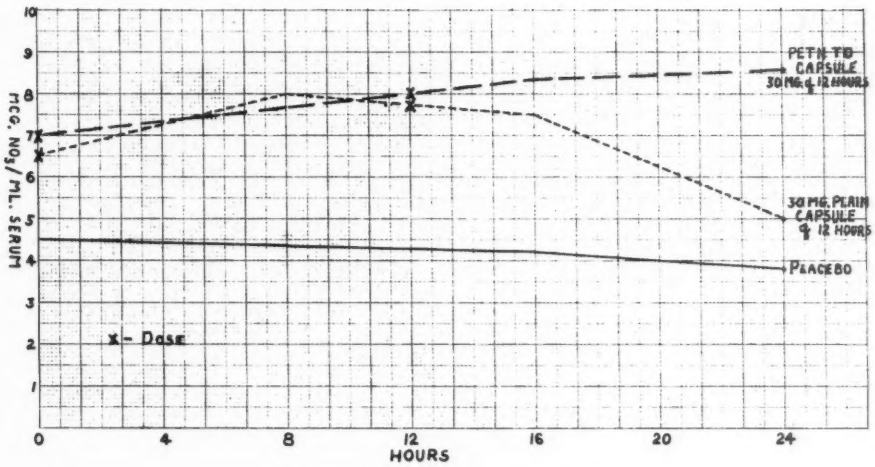


FIG. 3. Double blind test, 6 cases.

collected at variously spaced timed intervals for 24 hours. The blood nitrate curves obtained are shown in figure 3. The average range for the blood nitrates on the 2 patients receiving the placebo was 3.8 μg. per ml. to 4.5 μg. per ml. These values were in agreement with previous determinations. On inspection of the absorption nitrate curve (fig. 3) it is noted that the placebo curve differs from the diurnal curve previously shown on the "control" subjects. The explanation for this apparent discrepancy is the difference in the time of collection of the blood specimens. The specimens were collected at 4-hour intervals, in this experiment, rather than at 2-hour intervals (fig. 1).

The effect of PETN upon the nitrate blood levels is apparent in figure 3. The 2 patients receiving 30 mg. PETN, plain capsules, reached a peak nitrate level at 8 hours with a 24-hour level of 5.0 μg. per ml. being obtained. A difference in the curve of the blood nitrate levels is seen with the 2 patients receiving PETN-TD capsules. A smoothing out the blood nitrate absorption curve is noted, consistent with the more uniform release of the medication. In the latter 2 patients, the average peak intake level of 8.5 μg. per ml. was obtained 12 hours after the last dose of PETN-TD.

Observations on Cardiac Patients

The selected cardiac patients had been on PETN for at least 1 month, with good control of the symptom of angina pectoris. The dosage schedule for each patient was 20 mg. 4 times daily, before meals and at bed time. At the time of their hospitalization the medications were continued. The patients remained ambulatory on the wards and received the regular hospital diet during the 24-hour observation period. The regularly prescribed medication was given at bed time, usually between 10 and 11 p.m. The following morning, 7 to 8 a.m., an overnight blood specimen was drawn for subsequent nitrate analysis. This fasting specimen represented a 6- to 10-hour abstinence from the nitrate medication. Table 2 records the morning fasting nitrate values from the sera obtained on 10 patients who had received PETN, 20 mg. after meals and at bed time for 2 months. It is noted that the range of the individually determined nitrate levels is considerably greater than the nitrate levels obtained in the control group. Furthermore, the individual nitrate levels on the serum are higher, indicative of a cumulative effect for the chronically administered nitrate drugs.

Figure 4 illustrates the effects of PETN given in a timed dosage schedule on the blood

TABLE 2.—*Blood Nitrate Levels of Patients with "Chronic" Ingestion*

Subject	μg./n l.
A (Sehorski)	8.1
B (Vogel)	8.6
C (Sanders)	7.8
D (Divien)	8.1
E (Earls)	4.6
F (Frost)	9.2
G (Satisophalis)	5.2
H (Brerman)	6.2
I (Holmgren)	7.2
J (Rogers)	7.0
	Ave. 7.2

Range 4.6 to 9.2 μg. per ml.

nitrate levels of patients with coronary artery disease. Blood specimens were obtained every 2 hours during the day for subsequent nitrate analysis of the sera. The curve shown represents the average values for the sera nitrate determinations from 5 anginal patients given 10 and 20 mg. of PETN before their meals and at bed time. The picket-fence type of nitrate absorption curve is typical of that obtained with PETN tablets. The effect of the higher dosage schedule (20 mg.) is merely to exaggerate the peaks of the absorption curve. It is of interest that despite the drop or the fluctuation of the blood nitrate level, angina was not precipitated in these subjects during this experiment.

Figure 5 shows the results obtained from the sera of 10 patients with angina pectoris who were given a timed disintegrating capsule of 30 mg. of PETN administered at 12-hour intervals. The marked variations in the absorption curve seen with the PETN tablets is dampened and the resultant curve smoother. The observed nitrate levels fall within the range of 6 to 9 μg. of nitrate per ml. of serum. From our preliminary data we are of the opinion that a serum nitrate range of 6 to 9 μg. correlates with good control of the anginal syndrome.

A subjective trial of PETN-TD capsules was undertaken to evaluate a dosage schedule shown to provide a nitrate blood level of

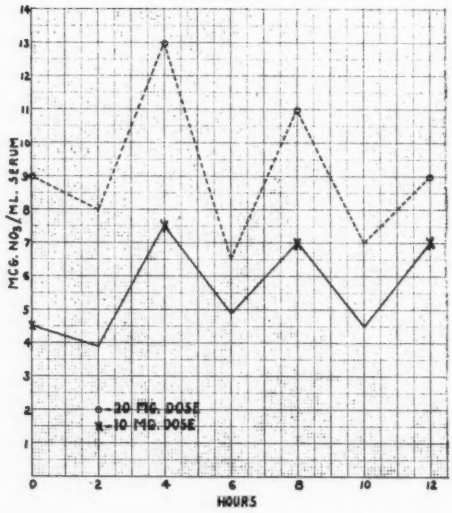


FIG. 4. Pentaerythritol tetranitrate tablets, 10 mg. or 20 mg., 4 times a day; 10 cases.

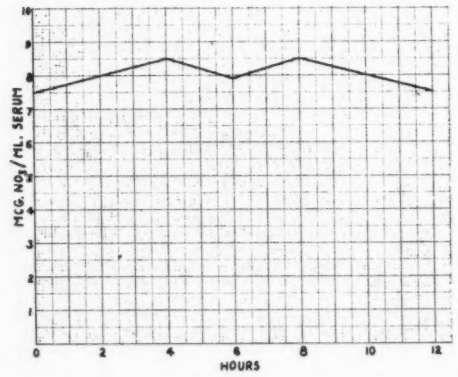


FIG. 5. Pentraerythritol tetranitrate TD capsule, 30 mg. every 12 hours; 10 cases.

between 6 to 9 μg. per ml. Sixteen patients with angina pectoris were selected from our out-patient department by the previously defined criteria. As accurately as possible, the anginal episodes of each patient were evaluated as to severity of pain, frequency of attacks, precipitating factors, exercise tolerance (subjective observations only; no Master tolerance tests were done), and good response to PETN tablets. Each patient kept a daily log of the character and number of attacks of angina that occurred, also

noting the precipitating factor. After 4 weeks of clinical observation the patients were switched from the PETN tablets to PETN-TD capsules, 30 mg.* every 12 hours, and continued to maintain a daily log. They were also asked to note any other effects of the capsules, especially drowsiness, anorexia, insomnia, lassitude, nausea, vomiting, or palpitations.

Subjective Observations

Fifteen of the 16 patients thought that the number and severity of their anginal episodes were generally decreased when they were placed on PETN therapy. Eight of the 16 who initially were started on 10 mg. of PETN, 4 times a day, noted a further improvement when the dosage was increased to 20 mg. of PETN 4 times a day. The side effects were limited to 3 patients who complained of gastric upset after taking the tablets.

On PETN-TD capsules, 14 of the 16 patients reported that their anginal episodes were further decreased in severity and frequency. It should be noted that these patients were receiving 2 30-mg. TD capsules (60 mg.) as compared to 4 20-mg. tablets or a total of 80 mg. of PETN daily. From these data it would appear that 60 mg. of PETN in TD capsule form is as effective as 80 mg. of PETN in tablet form, in controlling the anginal attacks.

Each PETN 30-mg. TD capsule included 50 mg. of secobarbital. Two patients complained that drowsiness was marked, but 8 patients preferred the capsules because they noted less "nervousness" and better ability to sleep. The remainder of the group (4 patients) did not note any effect of the barbiturate. The capsules were not associated with other side effects. Therefore, 12 of the 16 patients preferred the TD capsules, 3 of these noting further decrease in anginal episodes; 8 decreased "nervousness" attributable to the secobarbital, and all preferring the dosage schedule of 2 capsules per day to the 8 tablets daily of the plain PETN.

*Supplied as Corovas by Amfre-Grant, Inc., Brooklyn, New York. Manufactured by Victor M. Hermelin and Co., New Products Division of K-V Pharmacal Co., St. Louis, Mo.

Discussion

It is generally accepted that the nitrites are the only specific therapeutic coronary dilators for the treatment of angina pectoris.[17] Glyceryl trinitrate (nitroglycerin) is of proved value for the relief of the acute episodes of anginal pain. This relief is so dramatic that authors have incorporated the anti-anginal effect of nitroglycerin into their definitions of angina pectoris.[18] The prophylactic use of nitroglycerin has also been accepted by clinicians as being helpful in the management of coronary artery disease. Because of the subjective nature of angina pectoris it is admittedly difficult to assess the value of any medicament in the syndrome. Objective evidence supporting the role of the nitrates has been presented by Starr utilizing ballistocardiographic changes after nitroglycerin in patients with angina pectoris.[18] In these studies, the abnormal ballistocardiograms became more normal within 7 minutes after nitroglycerin was given, with dissipation of the effect by 15 minutes. The time effects of nitroglycerin correlate very closely to our own findings of the changes of the blood nitrates. It is logical to speculate that the ballistocardiographic changes can be attributable to the increase of nitrate blood level with its pharmacologic action on the coronary bed. Our studies would also indicate that a blood nitrate level of 6 to 9 μg. may be critical in the control of the anginal pain. Further observations along these lines are planned. We are particularly interested in correlating patients with poor control of the anginal attacks after nitroglycerin and PETN. It may well be that this small percentage of patients with angina pectoris may have some unknown failure to absorb the medication.

Summary

Nitrate blood levels can be influenced by nitroglycerin or pentaerythritol tetranitrate (PETN). There is an abrupt rise and fall

in nitrate blood levels following administration of each dose of PETN in tablet form. By combining PETN in timed-disintegration capsules, a more uniform release of the drug is obtained. PETN in timed-disintegrating capsule form provides a uniform, sustained release of the drug and a prophylactic effect for 10 to 12 hours' duration, in the treatment of angina pectoris.

Summario in Interlingua

Le nivellos de nitrato del sanguine pote esser influentiate per nitroglycerina o pentaerythritol tetranitrato (PETN). Il occurre un abrupte augmento e descendita del nivellos de nitrato del sanguine post omne administration de un dose de PETN in le forma de tablettas. Per includer PETN in capsulas a disintegration relentate, un plus uniforme liberation del droga es effectuate. PETN in iste modo de administration resulta in le uniforme e continue liberation del droga e in un effecto prophylactic de un duration de 10 a 12 horas in le tractamento de angina de pectore.

REFERENCES

1. Beecher, H. R.: Appraisal of drugs intended to alter subjective responses, symptoms. J.A.M.A. **158:** 339, 1955.
2. Cole, S. L., Kay, H., and Griffith, G. C.: Assay of anti-anginal agents. I. A curve analysis with multiple control periods. Circulation **15:** 405, 1957.
3. Silber, E. H., and Katz, L. N.: Coronary dilators and angina; reappraisal. J.A.M.A. **153:** 1075, 1953.
4. Gold, H.: Conference on therapy: How to evaluate a new drug. Am. J. Med. **17:** 722, 1954.
5. Rosenberg, H. N., and Michelson, A. L.: The use of pentaerythritol tetranitrate in chronic coronary insufficiency. Am. J. M. Sc. **230:** 254, 1955.
6. Kory, R. C., Townes, A. S., Maybe, R. E., Dorris, E. R., and Meneely, G. R.: Drug evaluation in angina pectoris: Khellin, Heperin and Peritrate. Am. Heart J. **50:** 308, 1955.
7. Windsor, T., and Scott, C. C.: Further observations of cardio-vascular effects of PETN in animals and man. Influence of pentaerythritol tetranitrate (Peritrate) on acute and chronic coronary insufficiency. Angiology **3:** 1, 1953. Am. Heart J. **49:** 414, 1955.
8. Feinblatt, T. M., and Ferguson, E. A.: Timed disintegration capsules — a further study. New England J. Med. **256:** 331, 1957.
9. Yogoda, H., Mitchell, J. H., Krayball, H. R., and Zscheile, F. P.: Quantitative spectro analysis of fats. Ind. and Eng. Chem., Anal. Ed., **15:** 1, 1943.
10. Speer, R. W., and Wright, G. H.: Colorimetric determinations of blood nitrate. To be published.
11. Russek, H. I.: Master two-step test in coronary artery disease. J.A.M.A. **165:** 14, 1957.
12. Master, A., Field, L., and Doroso, E.: Coronary artery disease and "The two-step exercise test." New York J. Med. **57:** 1051, 1957.
13. Roberts, J. T.: Continuous 24-hour vasodilation in the treatment of anginal pectoris. Clin. Med. **4:** 11, 1957.
14. Russek, H. I., Urbach, K. F., and Zohman, B. L.: Paradoxical action of Glyceryl Trinitrate (Nitroglycerin) in coronary patients. J.A.M.A. **158:** 1017, 1955.
15. —, Zohman, B. L., and Dorset, V. J.: Objective evaluation of coronary vasodilator drugs. Am. J. M. Sc. **229:** 46, 1955.
16. Russek, H. I., Zohman, B. L., Drumm, A. E., Weingarten, W., and Dorset, V. J.: Long acting coronary vasodilator drugs: Metamine Paveril, Nitroglyn, and Peritrate. Circulation **12:** 169, 1955.
17. Friedberg, C. K.: Diseases of the Heart. Ed. 1, Philadelphia. W. B. Saunders Co., 1950.
18. Starr, Issac, Pederson, E., and Corbascio, A. N.: The effect of nitroglycerin on the ballistocardiogram of persons with and without clinical evidence of coronary heart disease. Circulation **12:** 588, 1955.

Radiologic Aspects of Operable Heart Disease

VI. Changes Following Surgical Closure of Patent Ductus Arteriosus

By Philip Strauss, M.D., Herbert L. Abrams, M.D., and Saul Robinson, M.D.

The preoperative and postoperative radiologic findings in 71 patients with patent ductus arteriosus treated surgically were investigated. The purpose of the study was to determine the magnitude, character, and rapidity of the changes observed, as well as the relationship of the postoperative change to complicating cardiovascular lesions. Serial examinations were compared with the preoperative studies and with each other, including an analysis of over-all heart size, individual chamber size, the pulmonary vessels, and the aortic silhouette. The results were tabulated and their significance was evaluated.

THE preoperative radiologic findings in patent ductus arteriosus have been carefully studied and recorded.[1-3] Postoperative radiologic studies, on the contrary, have been few in number, although a number of allusions have been made to the changes noted after ligation.[1, 4, 5] As part of a continuing analysis of the radiologic aspects of operable heart disease, it seemed worthwhile investigating this matter in some detail, in an effort to determine the magnitude, character, and rapidity of the changes observed, as well as the relationship of postoperative change to complicating cardiovascular lesions.

Methods and Material

From a group of 165 consecutive cases of surgically corrected patent ductus arteriosus, 71 patients whose work-up included adequate preoperative and postoperative films were selected for analysis. All roentgen studies had been obtained in deep inspiration, and included posteroanterior, left anterior oblique, right anterior oblique, and lateral projections. Fluoroscopy was routinely employed, except in the immediate postoperative period.

In all cases, a left-to-right shunt through a patent ductus arteriosus was present, and closure of the ductus was undertaken surgically. The age of the patients at the time of surgery is indicated in table 1. Most patients were followed clinically and radiologically for a period of 1 to 5 years.

The clinical, laboratory, and operative findings were studied prior to radiologic analysis. Thereafter, 2 of the authors assessed on a scale of 0–4+ the size of the pulmonary artery segment, the central or hilar pulmonary arteries, the peripheral pulmonary arteries, the pulmonary veins, the aortic knob, the right atrium, right ventricle, left atrium, and left ventricle. The cardiothoracic ratio and the pulmonary-thoracic ratio* were measured on all preoperative and postoperative examinations. The presence or absence of a convexity at the caudal margin of the aortic knob was noted, and fluoroscopic findings were evaluated. Too few preoperative and postoperative kymograms were available for analysis in this series.

From the Departments of Radiology and Pediatrics Stanford University School of Medicine, San Francisco, Calif.

Results

Cardiothoracic Ratio

Cardiothoracic ratio† (C-T ratio) was greater than .50 in 52 patients, and less than .50 in 19. In 50 patients with a C-T ratio above .50, a significant decrease was apparent in the postoperative period (fig. 1). In 2, an increase in the C-T ratio occurred. Among the 19 patients with a ratio of less than .50, a significant diminution occurred in 15. All patients under 10 years of age with an un-

*The pulmonary-thoracic ratio constitutes the ratio of the spine-pulmonic arc distance in centimeters to the transverse diameter of the chest in centimeters (the spine-pulmonic arc distance is measured from the right lateral margin of the spine at the level of the pulmonary artery segment to the midpoint of an arc drawn at the lateral edge of the pulmonary artery segment, see figure 2).

†The cardiothoracic ratio, although a crude method of evaluating gross cardiac size, seemed useful in comparing preoperative and postoperative films on the same case. While it is true that the cardiothoracic ratio normally diminishes with age, the major change in our patients occurred within the first few months after surgery, and probably represents an effect of the operation.

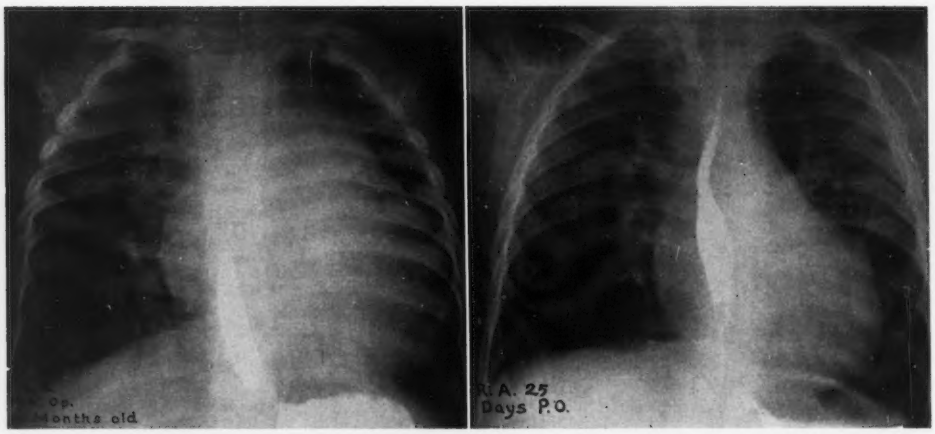


FIG. 1. Patent ductus arteriosus with gross cardiac enlargement. This 16-month-old boy had had many episodes of pulmonary edema prior to admission, and, in spite of medical therapy, congestive heart failure was uncontrollable. *Left.* Preoperative film. There is massive cardiac enlargement, which in oblique projections was shown to involve both ventricles and the left atrium. The pulmonary vascularity is increased, with large vessels seen at the right base and in the retrocardiac region as well. The aortic knob cannot be defined. The main pulmonary artery is remarkably prominent. *Right.* Twenty-five days after operation. A marked decrease in heart size and pulmonary vascularity has occurred. Subsequent films demonstrated further diminution in size.

TABLE 1.—*Age of Seventy-one Patients with Patent Ductus Arteriosus at Time of Surgery*

Age	No. of patients
6—23 months	7
24—59 months	21
5— 9 years	24
10—14 years	12
15 years and older	7
Total	71

complicated patent ductus demonstrated a decrease in the C-T ratio postoperatively.

Individual Chamber Size.

Left Ventricle. In 54 of 71 patients there was enlargement of the left ventricle preoperatively. In 45 of these cases, a definite diminution in left ventricular size, usually to normal, was noted during the postoperative observation period.

Left Atrium. Left atrial enlargement was present in 50 of 71 cases. In 40 of these, there was a return to normal size postoperatively. Among the cases showing no definite change, only slight preoperative enlargement had been present in 7.

Right Ventricle. Right ventricular prominence was frequently present. The right ventricle was thought to be enlarged in 50 cases preoperatively, and in 42 of these, it diminished to normal size postoperatively.

Right Atrium. Right atrial size was difficult to evaluate, particularly in the older age group. Of the 14 patients in whom some degree of right atrial enlargement was thought to be present, 6 were below the age of 23 months. When present, right atrial enlargement was accompanied by right ventricular enlargement.

Pulmonary Vessels

Pulmonary-Thoracic Ratio (P-T ratio). The P-T ratio seemed larger than normal in 60 per cent of cases.* In 56 patients, there was a diminution in the P-T ratio after surgery (fig. 2), and in 11 an increase.

Pulmonary Artery Segment. In 65 cases,

*The pulmonary-thoracic ratio in normal subjects ranges from .15 to .25. Age and sex produce no consistent alterations in the P-T ratio.

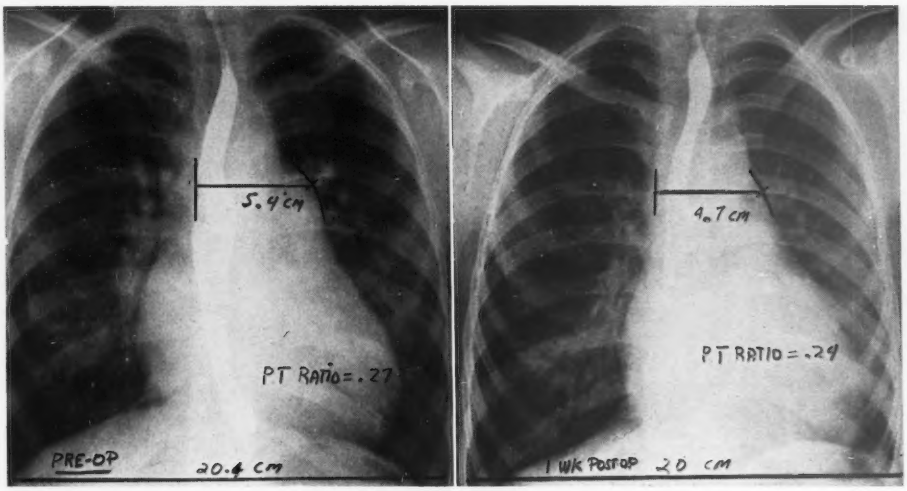


FIG. 2. Patent ductus arteriosus with large pulmonary flow. This 11-year-old girl had a pulmonary flow 4 times the systemic flow, and a mean pulmonary artery pressure of 57 mm. Hg. Following ductal closure, the mean pulmonary artery pressure dropped to 17 mm. Hg. *Left.* Preoperative film. The heart, pulmonary artery segment, pulmonary artery branches, and aortic knob are enlarged. The indentation of the barium filled esophagus is prominent. The pulmonary-thoracic ratio is .27. This figure is obtained by dividing (a) the distance in cm. from a line drawn at the right of the spine to a point intersecting the arc of the pulmonary artery segment (5.4 cm.) by (b) the transverse diameter of the chest (20.4 cm.). *Right.* One week after surgery. The pulmonary artery segment is no longer as prominent as before, the heart size is diminished, and the pulmonary vascularity is decreased. The pulmonary-thoracic ratio is now .24.

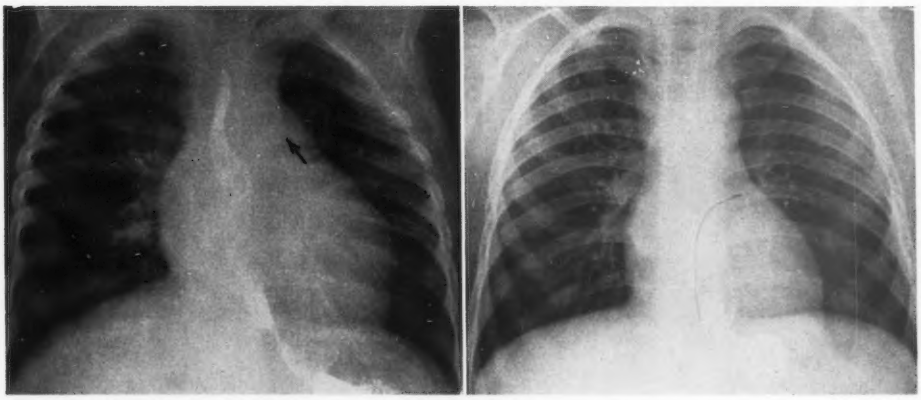


FIG. 3. Patent ductus arteriosus with aortic knob convexity in a 4-year-old boy. *Left.* Preoperative film. There is cardiac enlargement, prominence of the pulmonary artery segment, and increased vascularity. The aortic knob presents a convexity at its caudal surface (*arrow*). *Right.* Film obtained 1 year after operation. The bulge in the aortic knob is still visible, and if anything may be somewhat more prominent. The heart and pulmonary vessels have returned to normal size.

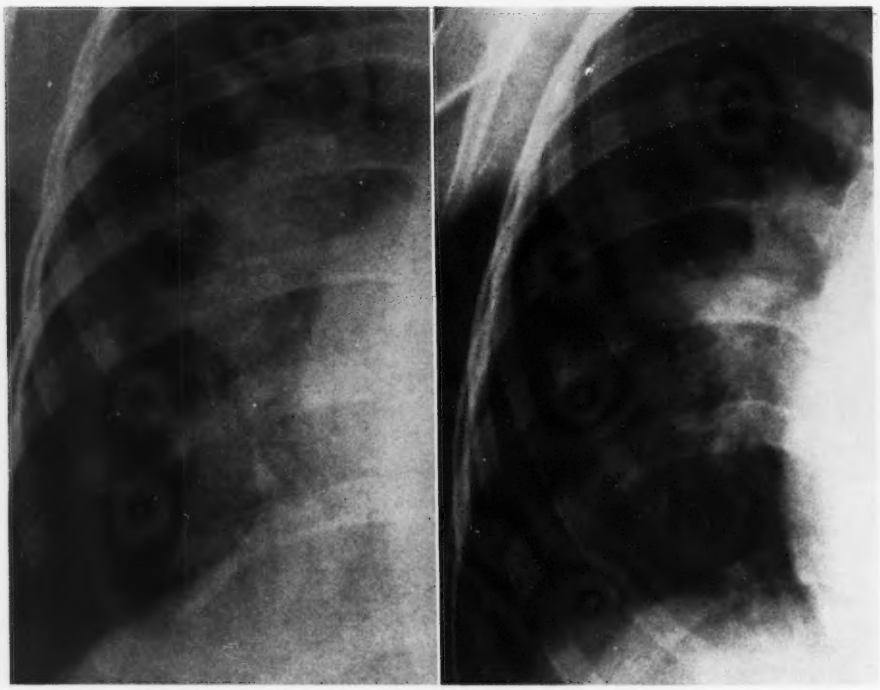


FIG. 4. Patent ductus arteriosus with decreased vascularity shortly after surgery. *Left.* Preoperative film. Note the marked increase in central pulmonary artery size, as well as in the size of the peripheral vessels. *Right.* Twelve hours after surgery. A remarkable decrease in the size of the pulmonary vessels has occurred within a short time following surgery.

the pulmonary artery segment was thought to be unduly prominent. Forty-eight of these demonstrated a definite reduction in the prominence of this segment postoperatively. In 17, no change was observed, and in one the pulmonary artery segment became larger.

Central Pulmonary Arteries. In 65 cases, the central (or hilar) pulmonary arteries were increased in size. In 56 of these, a postoperative return to normal was demonstrated.

Peripheral Pulmonary Arteries. In 56 cases, enlargement of the peripheral pulmonary arteries was noted. In all but 2 of these, a diminution in peripheral vascularity was observed postoperatively.

Pulmonary Veins. Evaluation of the size of the pulmonary veins was far more difficult than recent studies might indicate.[6] Enlargement of the pulmonary veins was thought to be present in only 14 cases. When the pulmonary veins were enlarged preoperatively, not infrequently their enlargement persisted during the postoperative period.

Aorta

Aortic Knob. Thirty-eight of 71 cases had a prominent aortic knob. In infancy and the early years of life, the aortic knob was difficult to distinguish, and was rarely prominent to a significant degree. In the older groups of patients, however, when the aortic knob could be well delineated, it usually appeared prominent. Following surgery, the aortic knob did not diminish significantly in prominence in most cases, and, in fact, particularly in the younger age groups became more prominent.

Aortic Knob Convexity Sign. A convexity just below the aortic knob has been described by Jönsson[7] as a sign of patent ductus arte-

FIG. 5. Patent ductus arteriosus with pulmonary hypertension and markedly elevated pulmonary resistance. This 11-year-old girl had marked pulmonary hypertension, with a pulmonary artery pressure of 99/64, and small bidirectional shunts. The calculated pulmonary resistance was elevated. Following closure of the ductus arteriosus, there was a poor response with intermittent right-sided congestive heart failure persisting over a sustained period of time. She died 10 months after operation in right heart failure. *Left.* Preoperative film. There is cardiac enlargement, a large main pulmonary artery, and prominent central pulmonary artery branches. The peripheral pulmonary branches are relatively small. *Right.* Film obtained 7 months after operation. There has been a marked increase in heart size, and an increase as well in the size of the central pulmonary arteries. The clarity of the peripheral lung fields is relatively striking, and the disparity between central and peripheral vessel size is an indication of the increased resistance in the peripheral pulmonary arterial bed.

TABLE 2.—*The Aortic Knob Convexity Sign in Patent Ductus Arteriosus*

Age	Total no. of patients	Patients with the sign	
		No.	per cent
6—23 months	7	0	0
2— 4 years	21	4	19
5— 9 years	24	8	33
10—14 years	12	5	42
15+ years	7	4	57
Totals	71	21	

riosus (fig. 3). This bulge is caused by the "infundibulum" of the ductus or the "ductus diverticulum."

This sign was more prominent in the older age groups than in the younger age groups (table 2). In 20 per cent of cases, it became more pronounced postoperatively than it had been preoperatively, and in some instances it became visible postoperatively when it had not been detected preoperatively.

Rapidity of Change

In the immediate postoperative period, the most striking changes observed are a decrease in the peripheral pulmonary vascularity and at times in the size of the hilar pulmonary arteries (fig. 4). Within a matter of hours after surgery, the vessels appear significantly less distended, and by 2 days they have undergone striking regression in size. Two months after surgery, the vessels may appear virtually normal, and beyond 6 months, little alteration in their size may be expected.

The heart size changes at a slower rate. A few days after surgery, some decrease in size may be noted. By 10 days postoperatively, the cardiac silhouette has usually diminished

somewhat in size, and by 2 months the major change in heart size has already occurred. At 6 months, the heart size has stabilized itself at a point which is rarely changed to any significant degree over the ensuing years. The magnitude of the change is proportional to the preoperative cardiac and pulmonary artery size, which, in turn, probably reflect the volume of the left-to-right shunt. Too few of the patients in this series were catheterized to allow an exact correlation between the size of the shunt and the preoperative appearance of the heart. There was a rough correlation between the size of the ductus as recorded by the surgeon and the degree of preoperative and postoperative roentgen change observed.

Effect of Pulmonary Hypertension

If the pressure is high, the shunt large, and the resistance normal or only slightly increased, the pulmonary arteries and heart size return to normal shortly after ductal closure. If the shunt is moderate and the resistance is increased moderately, the heart and pulmonary arteries may decrease in size, but not always to normal. If the shunt is small and the resistance markedly increased, no change in heart size or the appearance of the pulmonary arteries need occur, and indeed progressive enlargement with death in right heart failure may develop (fig. 5).

Complicating Lesions

In 13 of the 71 cases, complicating lesions were thought to be present postoperatively either on clinical grounds or on the basis of cardiac catheterization. These consisted of cardiac septal defects, aortic valvular disease, and, in 1 instance, pulmonic stenosis. In general, these were precisely the cases that failed to have the expected alterations in over-all heart size, individual chamber size, and pulmonary artery size during the initial 6-month postoperative observation period.

During the course of study, an apparent correlation between the incidence of second cardiac lesions and the presence of rubella early in pregnancy was incidentally observed. Of 11 patients whose mothers offered a history of rubella early in pregnancy, 6 had definite or very probable second cardiac or great vessel defects. Among 60 cases without a history of maternal rubella, only 9 were thought to have second lesions. This difference is statistically significant.* It is of interest that in patients with a history of maternal rubella, an aortic valvular abnormality (aortic stenosis or aortic insufficiency or both) was the second lesion in almost all cases. Others have made a similar observation.[8]

Fluoroscopy

The major preoperative finding not detectable on roentgenographic examination was the increased amplitude of pulsation of the left ventricle and aorta. In a smaller number of instances, the pulsations of the pulmonary arterial branches were somewhat increased. Fluoroscopic examination after closure of the ductus demonstrated a distinct diminution in the amplitude of pulsation of the left ventricle.

Discussion

Donovan et al.,[1] found relatively little change in heart size following ductal closure in their series. Only 27 of their patients had postoperative films, however, and the period of roentgenologic follow-up was not described and may have been too short to detect maximal change. Others have noted significant change in heart size following surgery.[4, 5] Our own experience emphasizes the uniformity with which reduction in heart size may be expected following ductal closure, particularly in patients under the age of 10. Only rarely does any significant regression in heart size or pulmonary vascularity occur beyond 6 months following surgery.

In the roentgenologic follow-up of the postoperative ductus, the question may well arise as to whether or not a persistent murmur is of functional significance. If the cardiac size and the pulmonary vascularity have not returned to normal by 6 months after sur-

*The chi square of 6.56 indicates that these figures are significant at the 2 per cent level.

gery, the chances of a significant complicating lesion are relatively high. Under those circumstances further and specialized investigation is warranted.

Virtually all cases of patent ductus arteriosus in this series had definite cardiac enlargement early in life. That a selection factor may be implicated is obvious. Most cases coming to surgery in infancy were in heart failure, which necessitated hospitalization. Obviously, the shunt in these cases was large and the heart size and pulmonary vascularity reflected this.

Of major interest was the fact that many hearts considered "normal" in size preoperatively decreased to a smaller "normal" in size postoperatively. In these cases the ductus arteriosus increased the work load of the heart and caused it to be larger than it would have been in the absence of a left to right shunt, but still well within radiologically normal limits. Similarly, in some instances in which the size of the pulmonary vessels was thought to be within the normal range, a decrease in size was observed. A clinical parallel lies in the observation that many seemingly asymptomatic patients with patent ductus arteriosus experience increased exercise tolerance after ductal closure.

The presence of pulmonary hypertension in association with patent ductus arteriosus is not necessarily a poor prognostic sign, nor need it represent a real increase in pulmonary resistance. If the pulmonary flow is markedly augmented, the pressure may be significantly elevated in the pulmonary artery even though calculated pulmonary resistance is normal. In these cases, the central and peripheral arteries will be enlarged, and the appearance of the pulmonary arteries will suggest increased flow primarily. If the pressure is markedly elevated and the left-to-right shunt is small, this reflects an increase in pulmonary resistance that may imply a poor prognosis (fig. 5). When the pulmonary resistance is thus increased, the size of the central or hilar pulmonary arteries will be increased, but the peripheral pulmonary arteries will be small or normal in size. This disparity (which can be expressed as a high ratio of central to peripheral artery size) is itself suggestive of pulmonary hypertension associated with elevated pulmonary resistance.[9]

In a recent attempt to evaluate the roentgen manifestations of pulmonary hypertension in congenital heart disease, Keats et al.[10] were able to find a significant disparity (2 − 3+) in respective sizes of central and peripheral arteries on only 14 of 36 cases. A slight (1+) disparity was noted in an additional 9 cases. In their study, however, all patients with pulmonary artery pressure ranging from 30 to 130 mm. Hg were considered as a single group, without considering age (3 to 45 years) or defining pulmonary blood flow or resistance. Under these circumstances, equivocal conclusions might have been predicted because (a) the disparity is a reflection of increased resistance[9, 11] rather than increased pulmonary flow, and (b) the central pulmonary arteries need not appear enlarged radiologically in children with increased pulmonary resistance*[9]

The fact that patients with patent ductus arteriosus and markedly elevated pulmonary resistance may do poorly following ductal closure is best illustrated by the experience with those patients who have reversal of flow.[12] Surgery in such cases is frequently followed by right heart failure and death. In cases in which the pulmonary resistance is known to be high, but in which some left-to-right shunt persists, attempts at surgical closure probably are justified, even though the prognosis is not as good as in the uncomplicated case. At surgery, and prior to definitive closure, a test period of ductus compression and careful observation of the dynamic changes that ensue is the best method of determining whether closure is practical or whether the patient's well being requires the ductus as an "avenue of escape."

The size of the aortic knob has been suggested as a differential point between patent

*It is of interest that the youngest case illustrated by Keats et al.[10] showing the disparity is a man of 34.

ductus arteriosus and cardiac septal defects.[3, 7, 13, 14] When a prominent aortic knob is visible, and the radiologic evidence of a left-to-right shunt is conclusive, this sign may be useful in suggesting that a patent ductus arteriosus is more likely than a ventricular septal defect. Its absence, however, should not militate against the diagnosis of a patent ductus arteriosus. This is particularly true in the younger age group, in whom a prominent aortic knob is rarely visible. Above the age of 10, in most instances the aortic knob is prominent and is therefore a more useful diagnostic point at this age. Reliance on the presence of aortic convexity at the site of the ductus is unwarranted in the younger age group, since it is rarely detectable below the age of 4. Above the age of 10 its presence is helpful, but its absence is of no significance in excluding the presence of a patent ductus arteriosus. It was of interest that this sign became significantly more prominent in a number of cases after closure of the ductus. This seemed to be associated with a diminution in the size of the pulmonary artery segment, and hence a sharper delineation of the aortic knob than had previously been possible.

Summary and Conclusions

Seventy-one cases of patent ductus arteriosus in which surgical therapy was undertaken were analyzed radiologically preoperatively and postoperatively.

A definite diminution in heart size and pulmonary vascularity was observed in a large majority of uncomplicated cases. The most striking early change was in the size of the pulmonary arteries. The diminution in heart size occurred over a somewhat longer period of time.

If the heart size and pulmonary vascularity fail to return to normal by 6 months, a complicating lesion should be suspected.

The aortic knob does not appear enlarged in a significant number of infants with patent ductus arteriosus. Following surgical closure of the ductus, the prominence of the knob may increase significantly.

Summario in Interlingua

Septanta-un casos de patente ducto arteriose esseva analysate radiologicamente ante e post le intervention chirurgic.

In le grande majoritate del casos non-complicate, un definite reduction del dimensiones cardiac e del vascularitate pulmonar esseva observate. Le plus frappante alteration de occurrentia precoce concerneva le dimension del arterias pulmonar. Le diminution del dimensiones cardiac occurreva in le curso de periodos un pauco plus longe.

Quando le dimension cardiac e le vascularitate pulmonar non retorna al stato normal in le curso de 6 menses, le suspicion de un lesion complicatori es justificate.

Le button aortic se monstra non-allargate in un numero significative de infantes con patente ducto arteriose. Post clausion chirurgic del ducto, le prominentia del button pote accentuar se de maniera significative.

References

1. Donovan, M. S., Neuhauser, E. B. D., and Sosman, M. C.: The roentgen signs of patent ductus arteriosus. A summary of 50 surgically verified cases. Am. J. Roentgenol. **50**: 293, 1943.
2. Keats, T. E., and Steinbach, H.: Patent ductus arteriosus. A critical evaluation of its roentgen signs. Radiology **64**: 528, 1955.
3. Nichol, A. D., and Brannon, D. D.: The differentiation of patent ductus arteriosus and atrial septal defect. Am. J. Roentgenol. **58**: 697, 1947.
4. Gross, R. E.: The patent ductus arteriosus: observations on diagnosis and therapy in 524 surgically treated cases. Am. J. Med. **12**: 472, 1950.
5. Lynxwiler, C. P., and Wells, C. R. E.: Patent ductus arteriosus: a report of 180 operations. South. M. J. **43**: 61, 1950.
6. Steinbach, H. L., Keats, T. E., and Sheline, G. E.: The roentgen appearance of the pulmonary veins in heart disease. Radiology **65**: 157, 1955.
7. Jönsson, G., and Salzman, G. F.: Infundibulum of patent ductus arteriosus. A diagnostic sign in conventional roentgenograms. Acta radiol. **38**: 8, 1952.
8. Bonham-Carter, R. E., Walker, C. H. M., Daley, R., Mathews, M. B., and Medd, W. E.: Patent ductus arteriosus with an abnormal aortic valve. Brit. Heart J. **17**: 255, 1955.

9. Abrams, H. L.: Roentgenologic aspects of increased pulmonary artery pressure and flow: preliminary observations. Stanford M. Bull. **14**: 97, 1956.
10. Keats, T. E., Kreis, V. A., and Simpson, E.: The roentgen manifestations of pulmonary hypertension in congenital heart disease. Radiology **66**: 693, 1956.
11. Ebnother, C., and Abrams, H. L.: Radiologic aspects of the Eisenmenger complex. Am. J. Roentgenol. **77**: 248, 1957.
12. Anderson, R. C., Adams, P., Jr., and Varco, R. L.: Patent ductus arteriosus with reversal of flow. Clinical study of ten children. Pediatrics **18**: 410, 1956.
13. Bruwer, A. J.: Practical value of the postero-anterior roentgenogram and roentgenoscopy in certain types of heart disease. Am. J. Roentgenol. **76**: 664, 1956.
14. Margulis, A. R., Figley, M. M., and Stern, A. M.: Unusual roentgen manifestations of patent ductus arteriosus. Radiology **63**: 334, 1954.

Jolliffe, N.: Fats, Cholesterol, and Coronary Heart Disease. New York State J. Med. **57**: 2684 (Aug. 15), 1957.

The environmental factor that correlates best with coronary heart disease is total fat consumption when expressed as a per cent of the total calories. This relationship between total fat intake and coronary heart disease rates for men below 65 may be expressed as follows: populations with fat intakes approximating 40 per cent of their total calories have high death rates; populations with total fat intakes below 20 per cent of total calories have low death rates; populations with intermediate fat intakes have intermediate death rates. Although there are degrees of susceptibility mediated by such unalterable factors such as sex, race, heredity, and body constitution and other environmental factors such as physical activity, obesity, and excessive tobacco, it is clear that the amount and type of fat intake is a major etiologic factor in the pathogenesis of coronary heart disease. Several groups of observers have conclusively demonstrated that feeding diets consisting of highly saturated fats results in high levels of blood cholesterol. Substitution or addition to the diet of certain oils, all naturally rich in unsaturated fatty acids, results in a consistent fall of serum and β-lipoprotein total cholesterol. A deficiency of unsaturated fatty acids, particularly of the essential linoleic, linolenic, and arachidonic acids, results in the formation of a saturated fatty acid-cholesterol complex. This is deposited to a greater extent in the intima of high-pressure arteries. These deposits in the aorta or other large vessels are relatively innocuous but when they are deposited in a strategic position in a coronary vessel, an occlusion or thrombosis may occur. The demonstration that feeding certain marine and vegetable oils containing unsaturated fatty acids causes a fall in serum and β-lipoprotein total cholesterol levels constitutes a major breakthrough for public health that may prove of practical value.

Harris

Pulmonary Compliance in Patients with Periodic Breathing

By HAROLD A. LYONS, M.D., FRANK BURNO, M.D., AND RICHARD W. STONE, M.D.

A study of pulmonary compliance in patients with periodic breathing was made. The elastic properties of the lung were found to be normal in some patients and grossly decreased in others. Two types of periodic breathing mechanics were found: in one there are similar variations of tidal volumes and unchanged pulmonary compliance; in the other a constant fluctuation of the intraesophageal pressure associated with the variations in tidal volume.

CHEYNE, a professor in Dublin, reported a description of the breathing of one of his patients. "For several days his breathing was irregular; it would entirely cease for a quarter of a minute, then it would become perceptible, though very low, then by degrees it became heaving and quick a minute during which there were thirty acts of respiration." This was the first clinical description of periodic breathing.[1] Thirty-six years later Stokes[2] described similar breathing in a patient of his own. "For more than two months before his death, this singular character of respiration was always present, and so long would the periods of suspension be, that his attendants were frequently in doubt whether he was not actually dead. Then a very feeble, indeed barely perceptible inspiration would take place, followed by another somewhat stronger, until at length high heaving, and even violent breathing was established, which would then subside till the next suspension. This was frequently a quarter of a minute in duration . . . " Twenty-four years later Traube advanced the first noteworthy theory of the mechanism of Cheyne-Stokes breathing.[3] He described 2 types of Cheyne-Stokes breathing, namely that with an intracranial lesion in the presence of an intact heart, and that with cardiac disease but no change in the brain. He believed that a diminished arterial blood supply to the brain was the pathogenic factor common to both types, this decreased cerebral blood supply causing a diminished respiratory center activity.

Since then, the condition of periodic breathing has been the subject of numerous reports. However, in the investigation of the abnormal state, attention must be given to the original description of a definite period of apnea in which the length of the cycle must be 1 minute. There has been a tendency to call all forms of periodic breathing, Cheyne-Stokes, without regard to the description found in the first reports. Christie and Hayward[4] suggested that the type of periodic breathing found in patients with left ventricular failure was due to a waxing and waning pulmonary congestion. They based this opinion on observations of measurements of intrapleural pressures and tidal volumes made on anesthesized cats and rabbits. They found that although the tidal volume underwent cyclic changes, the intrapleural pressure remained constant. These findings could only be interpreted as being due to cyclic changes in the mechanical properties of the lungs. If the origin was of involvement of the respiratory center, then the intrapleural swings should also show similar cyclic changes.

Eyster[5] has pointed to the differences in the two forms of periodic breathing. He observed when depression of the respiratory center occurs, the blood pressure rises during the apneic phase and falls during the hyperpnea, while the reverse is found in patients with periodic breathing associated with cardiovascular disease. It has been noted clinically that the cycle is longer in

From the Department of Medicine, State University of New York, Downstate Medical Center, Brooklyn, New York, and the Kings County Hospital Center, Brooklyn, N. Y.

This study was aided by a contract with the Office of Naval Research and State University of New York.

periodic breathing associated with cardiovascular disease, and that the fluctuations in resting end-expiratory level do not occur in the central type. The response to oxygen inhalation is also of interest for the periodic breathing of cerebral origin will be abolished, whereas that due to cardiovascular disease usually will not be affected, or it may, in fact, be exaggerated. Carbon dioxide inhalations will usually abolish the periodic breathing associated with cardiac disease, but will not affect that associated with a cerebral disturbance.

That changes in the activity of the respiratory center and prolongation of the circulation time are important factors in the production of Cheyne-Stokes breathing has been shown by recent studies.[6-8]

This report stems from a study of the mechanical properties of the lungs in patients with periodic breathing in whom an attempt was made to distinguish 2 mechanisms, a peripheral and a central type for periodic breathing. An attempt was also made to assess the role of the waxing and waning of pulmonary congestion as suggested by Christie and Hayward in their study.

Methods

The patients were all ill enough to make their cooperation difficult. All patients had to be studied either in the sitting position or semi-recumbent in bed. Those patients in whom satisfactory records for tidal volume were not obtainable were rejected from consideration in this study. Intraesophageal pressures were obtained with an air-filled balloon connected with a Statham gage similar to the previously described method.[9] Tidal volume was obtained by electronic integration of the air flow obtained through a pneumotachograph. All records were made simultaneously and recorded by photography of an oscillographic trace.* Breath-by-breath records of tidal volume and intraesophageal pressures were obtained throughout several cycles of periodic breathing in each patient.

The elastic behavior of the lungs may be stated in terms of compliance, an expression that relates changes in volume to changes in transpulmonary pressures when there is no flow of air:

$$\text{Pulmonary compliance} = \frac{\triangle \text{ volume, L.}}{\triangle \text{ pressure, cm. } H_2O}$$

*Electronics for Medicine Recorder.

By convention, in human subjects the ratio is determined from the end-expiratory relaxation volume (functional residual capacity).

Five patients with congestive heart failure who had Cheyne-Stokes respiration and whose studies were satisfactory were used in this study.

Clinical Summaries

S. O., a 55-year-old white man, was admitted to the hospital complaining of exertional dyspnea, paroxysmal nocturnal dyspnea, orthopnea, weakness, and fatigue. He had had a posterior myocardial infarction 6 months prior to admission, shortly after which the above symptoms began and progressed. His blood pressure was 94/80 mm. Hg, the pulse was 112 per minute and regular, the respirations were 40 per minute and of the Cheyne-Stokes type. The cervical veins were distended and bilateral basilar pulmonary rales were heard. The heart was enlarged to percussion and a gallop rhythm was present. The second pulmonic sound was louder than the second sound heard at the aortic area. The liver was enlarged and tender. The venous pressure was equivalent to 120 mm. of saline and the circulation (Decholin) was 36 seconds. Little variance in compliance was present throughout the cycle of his periodic breathing.

W. G. was a 27-year-old obese Negro man who gave a long-standing history of hypertensive cardiovascular disease. He was admitted in congestive heart failure. His weight was over 300 pounds. The blood pressure was 240/170, the pulse was 108 per minute and regular. The respirations were 40 per minute and of the Cheyne-Stokes type. Pulmonary rales, an enlarged heart with gallop rhythm and an enlarged tender liver with dependent edema were present. The pulmonary compliance was 0.05 L. per cm. of water throughout the entire Cheyne-Stokes cycle.

A. K. was a 45-year-old white woman with a history of rheumatic heart disease from an early age. Six months before admission there were several embolic episodes. Congestive heart failure for many years had been controlled by digitalis and salt restriction. At the time this patient was studied recent recurrences of cerebral embolization were present. There was aphasia and a left-sided hemiplegia. Classical signs of congestive heart failure were present. There was marked distention, pulmonary rales, and an enlarged liver with peripheral edema. Atrial fibrillation was present. The apical rate was 140 per minute. Pulmonary compliance was 0.10 L. per cm. of water. There was an absence of variation and pressure fluctuations following tidal volume changes.

E. D. was a 75-year-old white woman with a history of hypertension for many years. Nine months before admission a cerebral vascular accident had occurred. A left-sided hemiparesis re-

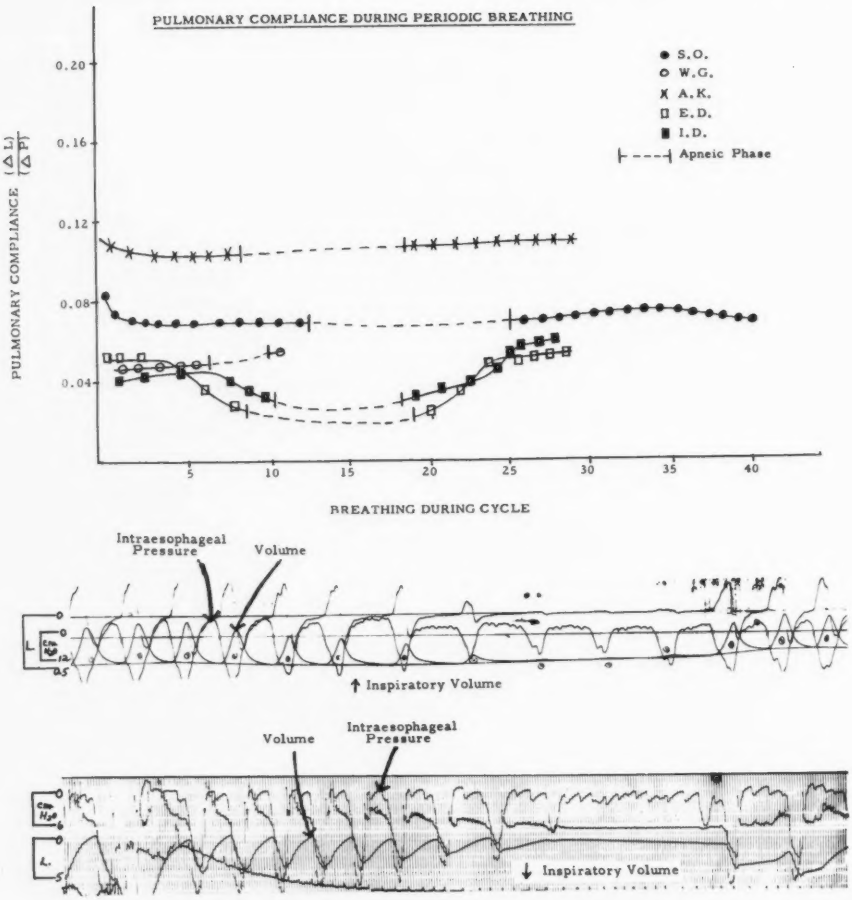


FIG. 1 *Top.* The average results of the 5 patients by breaths during the cycle and the change of pulmonary compliance during the cycle. It will be seen that the 2 lower curves show a fluctuation in the pulmonary compliance not observed in the other patients.

FIG. 2 *Middle.* The continuous tracing of the simultaneous recording of intraesophageal pressure, tidal volume and respiratory flow of patient A.D. It will be noted that the intraesophageal pressure fluctuations continue in the absence of tidal volume. A similar record was obtained for patient E.D. This represents a peripheral type of periodic breathing.

FIG. 3 *Bottom.* The continuous tracing of the simultaneous record of tidal volume, intraesophageal pressure fluctuations and air-flow in patient S.O. Inspiration is recorded downward. All of the records are at base line during the phase of apnea. This is the type of tracing exhibited by patients with the central type of periodic breathing.

mained. Progressive dyspnea, orthopnea, and left chest pain required her admission to the hospital. The blood pressure was 180/120; the pulse was 120 per minute and was regular. The thyroid gland was palpable. There were signs of severe congestive heart failure with a gallop rhythm being present. The pulmonary compliance was decreased ranging from 0.07 L. per cm. to 0.06 L. per cm. of water. This record showed a cyclic fluctuation during the phases of periodic breathing, becoming more decreased during apnea. The intraesophageal pressure fluctuations remained constant during the phase (figs. 1 and 2).

I. D. was a 55-year-old white woman who had hypertension and congestive heart failure for 2 years before admission. Digitalis and diuretics

were needed for left-sided failure. Her symptoms had progressively become worse for the past 6 months. On physical examination the blood pressure was 150/105, the pulse 100 per minute and regular. Distended cervical veins and bilateral rales at the bases of the lungs were present. The heart was found enlarged on percussion; the liver was palpable 6 cm. below the costal margin. Pretibial edema was found. Periodic breathing was present. The venous pressure was equivalent to 130 mm. of saline and the circulation time was 35 seconds. The pulmonary compliance was the lowest found among these patients, being 0.025 to 0.03 L. per cm. of water. In the records the fluctuation of the esophageal pressure remained constant throughout the cycle of periodic breathing, even during the phase of apnea. This was evidence of the force applied being ineffective to produce a change in lung volume in this phase of the cycle.

Results

Five patients of those studied had tracings satisfactory and complete enough to be analyzed. Two men and 3 women comprised the group. All had classical Cheyne-Stokes breathing. The period of apnea lasted 15 to 28 seconds and the cycle length was 40 to 69 seconds. In 3 patients, who were the only ones to whom aminophylline was administered after completion of the study, the periodic breathing was abolished.

The data obtained from the 5 patients are presented in figure 1. This is a graph of the average pulmonary compliance during a cycle of periodic breathing for each patient. Each curve is the mean curve of 2 to 3 measurements of separate cycles of periodic breathing for each patient. It will be seen that in 3 patients (S.O., W.G., and A.K.) no changes in the mechanical properties of the lungs during periodic breathing occurred even though 2 of them demonstrated an increased rigidity of the lungs. A.K. had a normal value for pulmonary compliance. In all these patients the pressure and volume tracings waxed and waned together. This type of trace indicates a periodic variation in the forces applied to the lungs, presumably central in origin due to cyclic variations in the respiratory center. The remaining 2 patients, however, as is seen in figure 1, did not show the periodic fluctuation in the pressure record and there was considerable variation in compliance. In patient A.D. there was a continuing pressure fluctuation during apnea, and the lung compliance became progressively less compliant for this period and became more compliant during hyperpnea. The simultaneous record of volume and pressure is shown in figure 2. This finding was identical to that found by Christie and Hayward in laboratory animals.[4] Patient E.D. also showed a periodic fluctuation in pulmonary compliance of the same type. In all these patients except A.K. there was increased lung rigidity. Three other patients with periodic breathing also had normal pulmonary compliance values. However, because of incomplete studies they were excluded from the final results. The record of S.O. is seen in figure 3.

Ear oximeter studies were made in 3 patients but are not pertinent to this discussion; they are mentioned only to state that the findings were similar to those of Gilmore and Kopelman, where the highest oxygen saturations are recorded during apnea and the lowest at hyperpnea.[7]

Discussion

Although 3 of these 5 patients gave no evidence of the waxing and waning pulmonary congestion suggested by the studies of Christie and Hayward,[4] 2 patients definitely did. The 3 patients all were severely ill and had marked evidence of pulmonary congestion and heart failure. In these patients the intraesophageal pressure records were compatible with extrapulmonary cyclic changes, namely from the respiratory center, and thus are of the central type of Cheyne-Stokes breathing.[3] The 2 patients I.D. and E.D. did, however, show the pattern reported by Christie and Hayward.[4] This finding is the peripheral type of Cheyne-Stokes breathing referred to by Traube,[3] where the intraesophageal pressure fluctuations remain constant in the presence of a tidal volume exhibiting periodic breathing. The suggestion of Christie and Hayward was that this was due to pulmonary

congestion waxing and waning. Unfortunately no hemodynamic traces were recorded by us. In these patients the nonelastic resistance was elevated fourfold in one and threefold in the other. It is possible that other mechanisms may contribute to this second type of periodic breathing than that suggested by Christie and Hayward. It is known that with pulmonary congestion surface tension plays a significant role in decreasing pulmonary compliance.[10, 11] A liquid-air interface in the alveolar units produces a lag of the change in volume to the applied transpulmonary pressure.[12] This effect has been found to be most marked in pulmonary edema. The intrapleural pressure may, because of this effect, not be great enough to effect inflation. But this factor alone cannot explain the reinflation that follows the apneic phase. Greene[13] observed 2 types of Cheyne-Stokes respiration: in one there was an unchanging end expiratory level and in the other there was a fluctuating level of the resting respiratory level. This observation was thought to distinguish the peripheral from the central type of periodic breathing. But progressive increase in airflow resistance was not evident from our study, and this abnormality, by itself, is insufficient to explain the periodic breathing with continuing intrapleural fluctuations. Inertness of the lung, if profound, might similarly become a factor, but the situation as found in periodic breathing does allow this to become a helpful explanation.[14] In experiments on normal subjects simulating periodic breathing not a single instance was found of continuing intraesophageal pressure fluctuations during voluntary apnea.

Wilson[15] in experiments with newborn rabbits, in spite of vigorous respiratory efforts and great diaphragmatic contractions, detected only negligible tidal flow. In dogs, while investigating the intrapleural pressures at different points in the chest, Fahri noted no change in tidal volume at the time changes in pleural pressure occurred.[16] Furthermore, these changes in pressure occurred even after the dogs had been killed, in some instances as long as 30 minutes after death. Neither of these separate observations in newborn rabbits and in dogs was explained. We also have no sound explanation to offer for the phenomenon. The possibility of soft tissue obstruction arises as an explanation for the peripheral type. But attention to the obstruction of the pharynx and laryngeal areas did not seem a factor in preventing the occurrence of tidal volume.

The effect of aminophylline, by its bronchodilatory action and by affecting the geometric arrangement of the bronchi, may actually reduce intrapulmonary factors as surface tension and air-flow resistance. Its other pharmacologic effects also must operate in abolishing periodic breathing.[17]

Summary

The elastic properties of the lung have been measured in 5 patients with periodic breathing. The pulmonary compliance was found to be normal in some patients with periodic breathing and grossly decreased in others.

Two types of periodic breathing were found: first, in 3 patients the intraesophageal pressure record showed variation similar to the tidal volume, without change in compliance during the different phases of the cycle of periodic breathing; second, in 2 patients there was a constant fluctuation of the intraesophageal pressure record and of the force applied, which was accompanied by variations in the tidal volume record during the different phases of the cycle (from apnea to hyperpnea).

These findings support the conclusion that there is a periodic breathing due to periodic fluctuations in the activity of the respiratory center and that there is another type that is due to peripheral factors. The peripheral factors are not well defined.

Summario in Interlingua

Le qualitates elastic del pulmon esseva mesurate in 5 patientes con respiration periodic. Illos se monstrava normal in certe patientes con respiration periodic e grandemente diminuite in alteres.

Esseva trovate 2 typos de respiration peri-

odic. (1) In 3 patientes le registration del pression intraesophagee exhibiva variationes simile al variationes del volumine de aere currente, sin alteration de elasticitate durante le diverse phases del cyclo de respiration periodic. (2) In 2 patientes il habeva un fluctuation constante del pression intraesophagee e del fortia applicate, e isto esseva accompaniate de variationes in le volumine del aere currente in le curso del diverse phases del cyclo (ab apnea a hyperpnea).

Iste constatationes supporta le conclusion que il existe (1) un typo de respiration periodic causate per fluctuationes in le activitate del centro respiratori e (2) un altere type que es causate per factores peripheric. Iste factores peripheric non es ben definite.

REFERENCES

1. Cheyne, J.: Dublin Hospital Reports **2**: 216, 1818.
2. Stokes, W.: Disease of the Heart and Aorta. London, Hodges and Dublin, 1854.
3. Traube, L.: Gesammelte Zur Theorie des Cheyne-Stokes' schen Athmungsphänomens. Berl. klin. Wehnschr. **11**: 185, 209, 1874.
4. Christie, R. V., and Hayward, G. W.: Periodic changes in respiratory depth by changes in the lung. J. Physiol. **102**: 88, 1943.
5. Eyster, J. A. E.: Clinical and experimental observations upon Cheyne-Stokes respiration. J. Exper. Med. **8**: 565, 1906.
6. Pryor, W. W.: Cheyne-Stokes respiration in patients with cardiac enlargement and prolonged circulation time. Circulation **4**: 233, 1951.
7. Gilmore, H. R., and Kopelman, H.: Cheyne-Stokes respiration: an oximeter study. Brit. M. J. **2**: 1439, 1954.
8. Guyton, A. C., Crowell, J. W., and Moore, J.: The basic oscillating mechanism of periodic breathing in cardiac failure. Circulation **12**: 717, 1955.
9. McIlroy, M. B., Mead, J., Selverstone, N. J., and Radford, E. P., Jr.: Measurement of lung tissue viscous resistance using gases of equal kinematic viscosity. J. Appl. Physiol. **7**: 485, 1955.
10. Von Neergaard, K.: Neue Auffassungen uber einen Grundbegriff der Atemmechanik die Retraktionskraft der Lunge abhangig von der Oberflachenspannung in den Alveolen. Ztschr. f. d. ges. exper. Med. **66**: 373, 1929.
11. Radford, E. P., Jr., Lescoe, N., and Mead, J.: Factors governing long-term (static) pressure-volume characteristics of the lungs. Fed. Proc. **13**: 114, 1954.
12. Mead, J., Whittenberger, J. L., and Radford, E. P., Jr.: Surface tension as a factor in pulmonary-volume hysteresis. J. Appl. Physiol. **10**: 191, 1957.
13. Greene, J. A.: Clinical studies of respiration. IV. Some observations on Cheyne-Stokes respiration. Arch. Int. Med. **52**: 454, 1953.
14. Mead, J.: Measurement of inertia of the lungs at increased ambient pressure. J. Appl. Physiol. **9**: 208, 1956.
15. Wilson, J. L.: Physiology of the initiation and continuation of breathing after premature birth. Respiratory problems in the premature infant. Report of 15th *M.* and *R.* Pediatric Research Conference, 1955, pp. 42-45.
16. Fahir, L., Otis, A. B., and Proctor, D. F.: Measurement at different points in the chest of the dog. J. Appl. Physiol. **10**: 15, 1951.
17. Starr, I., Gamble, C. I., Margolies, A., Donal, J. S., Jr., Joseph, J., and Eagle, E.: A clinical study of the action of ten commonly used drugs on cardiac output, work and size; on respiration, on metabolic rate and on the electrocardiogram. J. Clin. Invest. **16**: 799, 1937.

Anomalous Origin of the Left Coronary Artery

The Physiologic Defect and Suggested Surgical Treatment

By Robert B. Case, M.D., Andrew G. Morrow, M.D., F.A.C.S., Wendell Stainsby, Sc.D., and John O. Nestor, M.D.

Anomalous origin of the left coronary artery from the pulmonary artery is a rare and almost universally fatal form of congenital heart disease. It has usually been assumed that flow in the aberrant artery is from the pulmonary artery toward the myocardium and efforts at surgical correction have been directed at increasing the perfusion pressure or the oxygen content of pulmonary artery blood. Evidence is presented, that flow in the aberrant artery is *into* the pulmonary artery and that ligation of the vessel at its origin should be carried out before irreversible myocardial damage has occurred.

IN 1911 the anomalous origin of the left coronary artery from the pulmonary artery was first described.[1] More than 50 such patients have subsequently been reported, and several reviews of the subject have appeared.[2–4] Only recently, however, has consideration been given to possible methods for the surgical correction of this rare defect.

The great majority of infants born with an anomalous left coronary artery die within the first year of life. However, there has been a number of recorded instances of this anomaly in individuals living to adult life.[5] Most were without symptoms of heart disease, although 2 suffered from angina pectoris for several years. In the adult group, death was usually sudden and occurred at a mean age of 35 years.

Eidlow and McKenzie[6] were apparently the first to diagnose the malformation during life. In 1946 they described a 3-month-old infant who exhibited attacks of dyspnea, cyanosis, pallor, and sweating that lasted several minutes and usually followed feeding. The heart was greatly enlarged and an electrocardiogram showed inversion of the T waves in leads I and II. The origin of the left coronary artery from the pulmonary artery was confirmed at autopsy.

Pathologic studies have shown that the aberrant vessel is thin walled and grossly vein-like in character. Histologically the vessel has an arterial structure in which there is atrophy of the media. The left ventricle is dilated and there is frequently thinning with scarring of that portion of the left ventricle supplied by the anterior descending coronary artery. There may, additionally, be uniform dilatation of the involved portion of the myocardium, although localized aneurysmal formation is not a common feature. Removed from the scarred portion of the myocardium, there is hypertrophy that frequently is responsible for increase in cardiac weight to as much as 4 times above normal. The endocardium of the left ventricle is usually thickened and resembles that seen in endocardial fibroelastosis.

In contrast to the majority of patients with anomalous left coronary artery are those with a single coronary artery arising from the aorta. This defect is almost never responsible for myocardial ischemia, cardiac enlargement, or electrocardiographic abnormalities. Such patients have a normal life span in the absence of other cardiovascular anomalies.[9]

The admission of an infant with an aberrant left coronary artery to the National Heart Institute prompted a survey of the possibilities of surgical treatment. The findings in the reported patients who had survived to adult life with the anomaly gave no clear indication as to why they had escaped death in infancy. Grossly visible anastomoses between the right and left coronary arteries

From the National Heart Institute, National Institutes of Health, Bethesda, Md.

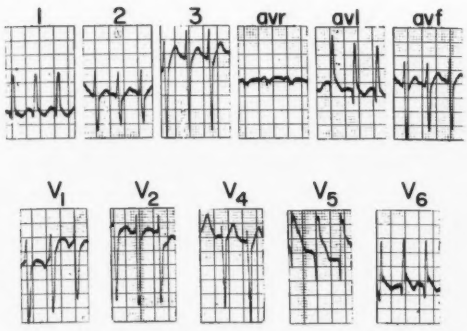


FIG. 1. Electrocardiogram of patient D. D. at 9 months of age. There is elevation of the S-T segment in aV_L, V_5, and V_6 indicating apical infarction. The tracing also shows peri-infarction block.

were present in several of these patients and absent in others. It is of importance that no perfusion or injection studies were performed on the hearts of these patients.

In most pathologic reports, it was assumed that blood flow was from the pulmonary artery into the anomalous vessel. Under these circumstances the low oxygen content and the low pressure of the pulmonary arterial blood were considered to be the main physiologic defects. A low coronary perfusion pressure will result in coronary insufficiency, as in clinical and experimental shock;[10, 11] however, low oxygen content of coronary arterial blood is not of major concern. In congenital heart disease of the cyanotic type, for example, coronary insufficiency is rare. The normal coronary vascular bed is able to compensate for a decreased arterial oxygen content by dilating and increasing coronary flow up to 500 per cent.[12] Hence it was considered that the creation of a normal perfusion pressure in the aberrant coronary artery would result in an adequate coronary circulation in spite of the low oxygen content. The creation of supravalvular pulmonic stenosis as described by Muller[13] was a means of effecting this increase in pressure. This operation in effect would substitute the benign prognosis of mild pulmonic stenosis for the grave one of aberrant coronary artery. As this procedure was being planned for case 1, a report by Kittle, et al.[2] was

FIG. 2. Selective angiocardiogram of patient D. D., lateral projection. The right ventricular outflow tract and pulmonary artery are well opacified but the anomalous coronary artery does not fill.

drawn to our attention. After similar reasoning, these authors had planned to create pulmonic stenosis in an infant with an aberrant left coronary artery. However, irreversible ventricular fibrillation occurred at the time of thoracotomy and the operation could not be completed.

CASE REPORTS

Case 1

D. D., a female infant had an episode of shortness of breath, pallor, and crying at age 3 weeks. The attack lasted for 15 to 20 minutes. A second attack of similar nature occurred at age 2½ months. At 2 months of age, x-rays showed cardiac enlargement both to the right and left, but no murmur was heard. An electrocardiogram at 3 months showed the pattern of anterolateral myocardial infarction. In addition to the abnormal T forces and the abnormal Q area, there was increased voltage of the QRS complexes, indicating left ventricular hypertrophy. Congestive heart

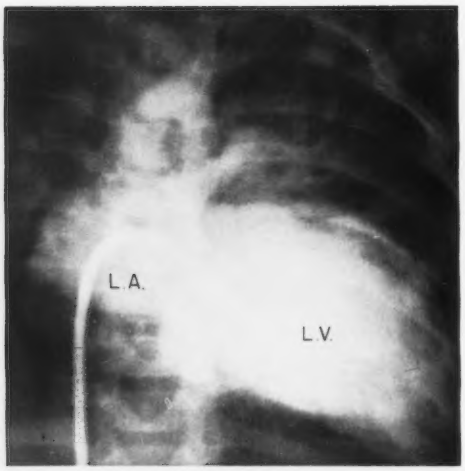


FIG. 3. Later films of the angiocardiogram of patient D. D., anterior projection. The left atrium and left ventricle are greatly enlarged and the wall of the ventricle is extremely thin.

failure occurred at 4 months; thereafter she was maintained on 0.2 ml. of Digalen daily.

At her first admission to the National Heart Institute on December 5, 1955, at age 8 months, her general physical development was poor. A rough, grade III systolic murmur was heard over the entire precordium, loudest at the fourth left intercostal space. The heart was enlarged to the left, pulsus alternans was present, and the liver was palpable. The electrocardiogram is shown in figure 1. It showed elevation of the S-T segment in aV_L, V_5, and V_6. A selective angiocardiogram with right ventricular injection was performed. The right ventricular systolic pressure was 55 mm. Hg. The outflow tract and pulmonary artery were well opacified and no filling of an anomalous coronary artery was evident (fig. 2). The left ventricle was dilated and thin walled (fig. 3). She was discharged in relatively good cardiac compensation with a diagnosis of anomalous left coronary artery on December 24, 1955.

In the ensuing 17 days, the child had a productive cough and episodes of crying and tachypnea. Congestive heart failure recurred and she was readmitted on January 10, 1956. The physical findings were essentially those of the first admission and, in addition, many fine inspiratory rales were heard at the lung bases. Pulmonary congestion was relieved by treatment with aminophylline and morphine. For the reasons discussed the production of supravalvular pulmonary stenosis was decided upon.

On January 24, 1956, during tracheal intubation following the induction of ether anesthesia, cardiac arrest occurred. The chest was opened immediately through a left anterolateral incision. Following cardiac massage, normal sinus rhythm returned and myocardial tone improved. The entire heart was seen to be markedly enlarged and a pale, fibrotic, elliptical area 6 cm. in diameter was seen on the anterior surface of the left ventricle. It was surrounded by a purplish area of myocardium quite different in appearance from the pinker areas of the right ventricle. A surgical stenosis was made in the main pulmonary artery and its lumen was reduced by about 60 per cent. During this procedure the heart appeared to fail on several occasions and its tone was improved by injections of calcium chloride. After completion of the stenosis, ventricular fibrillation occurred, which could not be permanently reverted.

Autopsy showed the left coronary artery to arise from the left cusp of the pulmonary artery and to bifurcate into the left anterior descending coronary artery and an abortive left circumflex artery. The right coronary artery was dilated and arose from the usual position. The left circumflex coronary artery anastomosed with the right coronary artery through a large loop-like vessel on the posterior surface of the left ventricle. There were many additional small vessels around the origin of the left circumflex artery, but their course could not be grossly determined. The ventricle was thin walled in the infarcted area and hypertrophied elsewhere. The endocardium of the left ventricle, especially on the septal surface, was opaque, white, and thickened.

Postmortem Perfusion of Heart. In order to determine the extent of anastomosis between right and left coronary arteries, perfusion studies were performed in which a catheter was tied into the pulmonary artery and another into the aorta. Motion pictures were taken as Evans blue dye was injected into the aortic catheter at a mean pressure of 100 mm. Hg. The dye appeared in the pulmonary artery catheter almost immediately, even while dye entering the myocardium was minimal and before it had spread beyond the base of the heart. This study indicated that there was free communication between the left and right coronary arteries near their origins. Also, the rapidity and profuseness of flow from the pulmonary artery catheter suggested that the path of least resistance to flow from the right coronary artery was into the pulmonary artery rather than into the myocardium. Hence, it was concluded that during life oxygenated blood passed via the extensive anastomotic channels from the right coronary artery into the left and then in a retrograde direction into the pulmonary artery.

Case 2

S. R., a Negro female, weighed 4 pounds, 12 ounces at birth following a 7-month gestation

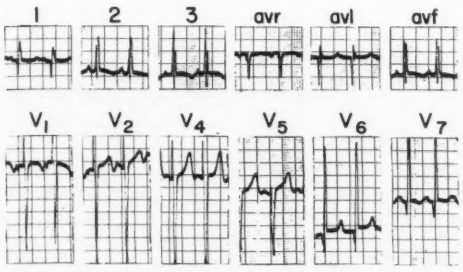


FIG. 4. Electrocardiogram of patient S. R. at 14 months of age. It is similar to that shown in figure 1 except that peri-infarction block is not seen.

period. Her development proceeded without event until age 14 months, when symptoms of bronchopneumonia appeared. Penicillin treatment was ineffective. An electrocardiogram taken at this time demonstrated a pattern suggestive of anterolateral infarction (fig. 4). Chest x-ray demonstrated an enlarged heart. She was digitalized with Digalen with relief of symptoms and has taken 0.2 ml. daily since that time.

Thereafter she was asymptomatic and continued to lead a normal, fairly active life. Because the electrocardiographic and clinical findings suggested an aberrant left coronary artery the patient was admitted to the National Heart Institute at the age of 19 months for evaluation. She was thin, well developed, and very active without respiratory distress. The heart was grossly enlarged to physical examination. A harsh, grade II systolic murmur was heard over most of the precordium, loudest at the fifth left intercostal space at the left sternal border. The liver was not enlarged.

It was considered that coronary arteriography would be diagnostic. A catheter was inserted via the femoral artery into the ascending aorta. Its tip was positioned just above the aortic valve and 8 ml. of 70 per cent sodium acetrizoate (Urokon) were injected. Biplane x-rays were taken at a rate of 6 per second. The right coronary artery was enlarged and was the only vessel seen to arise from the aortic root (fig. 5). The left coronary artery was visualized after 3 seconds by means of anastomoses between the 2 coronary arteries. The left coronary artery was much smaller than the right. Its site of origin was obscured by dye in the aorta. No dye could be seen in the main pulmonary artery.

A selective angiocardiogram with right ventricular injection was performed 1 month later. At this time the right ventricular systolic pressure was 40 mm. Hg. The outflow tract and pulmonary artery were normal, no aberrant vessel was filled from the pulmonary artery. The left atrial size was at the upper limit of normal. There were

FIG. 5. Coronary arteriogram of patient S. R. The right coronary artery (RCA) is much larger than normal. Numerous anastomotic channels are seen over the apex and the left coronary artery (LCA) fills from them.

dilatation and thinning of the left ventricular chamber. The diagnosis of anomalous left coronary artery was considered certain. Although operation was recommended, it was refused by the child's parents.

DISCUSSION

There now appears to be abundant evidence that flow through left coronary artery originating from the pulmonary artery is into the pulmonary artery rather than away from it. The possibility of retrograde flow occurring in the aberrant coronary artery was suggested by Edwards and Burchell,[14] after studying pathologic specimens. Dr. Edwards has also called to our attention a report published by Brooks in 1886[15] in which it was suggested that flow in an anomalous right coronary artery was into the pulmonary artery. This contention is borne out by the perfusion studies carried out in the heart of patient D. D., where it was demonstrated that large anastomoses allowed the free passage of blood from the right coronary to the left. Dr. D. C. Sabiston carried out similar perfusion studies in the heart of an infant with an anomalous

left coronary artery.[16] When the right coronary artery was perfused at a mean pressure of 70 mm. Hg, flow through it was 35 to 37 ml. per minute. With the left coronary subjected to a pressure of 15 mm. Hg, flow through it from the right was 2 ml. per minute. In this same heart the injection of contrast substance into the right coronary resulted in filling of the left and flow into the pulmonary artery. Similarly, the aortogram of patient S. R. showed filling of the left coronary from the right during life. In neither patient could the aberrant artery be filled by a selective injection of Urokon into the right ventricle, indicating again that flow was into the pulmonary artery. Flow into the pulmonary artery could not, however, be demonstrated in the aortogram, probably because of dilution of the contrast substance. Although the small left-to-right shunt into the pulmonary artery might be detected by the nitrous oxide test,[17] such studies have not been performed.

The source of the retrograde flow in the aberrant artery is from the normal right coronary artery through extensive anastomoses. Thus, although there is oxygenated blood in the left coronary artery, it does not reach the myocardium but passes instead into the low resistance circuit of the pulmonary artery. Additional clinical and pathologic evidence for this contention is contained in a recent publication by Jurishica.[5] He describes an 18-year-old patient with anomalous left coronary artery in whom a continuous murmur was audible over the precordium. A continuous thrill in the root of the pulmonary artery was also palpable at operation. Extensive anastomoses were demonstrated between the right and left coronary arteries at autopsy.

Thus, it would appear that ligation of the aberrant vessel at its origin would prevent retrograde flow and allow perfusion of the left ventricle by blood supplied through the anastomoses from the right coronary artery. This would in effect convert the anomaly into that of a single coronary artery arising from the aorta and supplying both ventricles. This possibility was first suggested by Edwards and Burchell[14] who stated: "It would seem proper to consider, if our reasoning is correct, whether therapy of anomalous origin of the left coronary artery from the pulmonary trunk should consist in interruption in continuity of the anomalous artery."

At the suggestion of the present authors, ligation of the aberrant coronary artery has been attempted in 3 patients. The first ligation was carried out by Drs. John Keith and W. Barnes of Toronto. At the time of ligation there was no change in the color of the myocardium or the size of the left anterior descending artery. The child died suddenly 10 hours postoperatively.

The second patient was operated upon by Major Edward Jehnke of the Walter Reed Army Hospital and will be reported in detail by him at a later date. The patient was a 4-month-old girl with electrocardiographic changes of anterior wall infarction. Immediately after ligation of the anomalous left coronary artery, the size of the anterior descending artery increased by 50 per cent and the left ventricular myocardium was pinker in appearance. The child did well in the immediate postoperative period and the electrocardiogram showed improvement, but she died 2 months later in cardiac failure. At autopsy the left ventricle was extremely thin and fibrotic, and death was attributed to irreversible myocardial damage.

A third infant, 4 months of age, was operated upon by Dr. Edgar W. Davis of Children's Hospital, Washington, D. C., on October 29, 1957. Following ligation of the anomalous artery at its origin the myocardial color and tone improved and the child has done well during the brief period thereafter.

Since the vast majority of infants with this anomaly die within the first year of life, operation should be carried out in all patients in whom the diagnosis is established. The procedure of choice would seem to be temporary occlusion of the anomalous artery at its origin from the pulmonary artery. If the vessels supplied by the aberrant become visibly larger, and the myocardium pinker, the

ligation should be made permanent. If these events do not occur, poor anastomoses between the 2 coronary arteries, is suggested, and an attempt should be made to create pulmonic stenosis. It is possible that ligation of the anomalous vessel may be the procedure of choice even though anastomoses are not evident, but this possibility must await further trial.

Other forms of surgical treatment have been suggested. These include de-epicardialization and pericardial poudrage,[16] transplantation or anastomosis of the anomalous vessel,[18] and excision of the infarcted area of the left ventricle.[18] Only the first of these procedures has been successfully accomplished.

Whether any surgical procedure will be of long-term value remains in doubt because of the severity of myocardial damage in most patients. However, any attempt at operative repair must be made at the earliest possible moment because of the progressive myocardial damage that occurs. When episodes of sweating, cyanosis, pallor, and abnormal crying (usually following feeding) appear in an infant, and are accompanied by gross cardiac enlargement and electrocardiographic evidence of myocardial ischemia, the diagnosis of anomalous coronary artery is suggested. Several conditions may simulate this defect and must be considered in the differential diagnosis.

The clinical picture is frequently identical in endocardial fibroelastosis but the Q waves are usually not so prominent and no QS waves are present. The left ventricle in fibroelastosis is usually hypertrophied and thick walled when visualized at angiocardiography. It is thin and dilated in the presence of an anomalous left coronary artery.

Severe aortic stenosis may also suggest left ventricular ischemia clinically. The classic murmur and thrill in the aortic area may not appear until later in childhood. Also, a systolic murmur is frequently heard along the left sternal border in an anomalous left coronary. (It was present in both cases reported herein.) The chief differential diagnostic features are the absence of a grossly enlarged heart and absence of deep Q waves across the left precordium in aortic stenosis. Again the angiocardiogram may be diagnostic. Acute glomerulonephritis, coarctation of the aorta, and patent ductus arteriosus are also to be considered. Rhabdomyoma and glycogen-storage disease are rare lesions that may be difficult to differentiate.

A definite diagnosis of anomalous coronary artery may be made by coronary arteriography. Selective angiocardiography is of value in excluding other lesions and in demonstrating the typically dilated and thin walled left ventricle.

Summary

Anomalous origin of the left coronary artery from the pulmonary artery is a rare and almost invariably fatal cardiovascular defect. The presumption has been that flow in the anomalous artery is *from* the pulmonary artery into the myocardium and treatment has been directed at either increasing the oxygen content of pulmonary arterial blood or its perfusion pressure. Clinical, physiologic, and pathologic evidence is presented, however, that flow in the anomalous vessel is *into* the pulmonary artery rather than away from it. The source of this retrograde flow has been shown to be from the normal right coronary artery through extensive anastomotic pathways. Thus, although oxygenated blood reaches the anomalous artery, the blood does not supply the myocardium but flows retrograde into the low resistance area of the pulmonary circulation. Ligation of the left coronary artery at its origin converts the lesion into that of a single coronary artery supplying both ventricles—a situation usually compatible with normal life expectancy.

Diagnosis of the defect by coronary arteriography is described and preliminary experience with the suggested surgical treatment is presented.

Summario in Interlingua

Le occurrentia de un arteria sinistro-coronari a origine anormal ab le arteria pulmonar es rar. Iste defecto cardiovascular es quasi

invariabilemente mortal. On ha supponite que le fluxo in le arteria anormal es *ab* le arteria pulmonar *a in* le myocardio, e le tractamento visava a augmentar le contento de oxygeno del sanguine pulmona-arterial o le fortia de su pression perfusional. Tamen, es presentate evidentia clinic physiologic, e pathologic que le fluxo in le vaso anormal es *verso* le arteria pulmonar e non *ab* illo. Il ha essite demonstrate que iste fluxo retrograde se origina ab le normal arteria dextero-coronari e passa per extense vias anastomotic. Assi, ben que sanguine oxygenate attinge le arteria anormal, le sanguine non alimenta le myocardio sed flue retrogrademente a in le area de basse resistentia representate per le circulation pulmonar. Le ligation del arteria sinistro-coronari al puncto de su origine transforma le lesion a in le stato de un sol arteria coronari que alimenta ambe ventriculos, e iste stato es usualment compatibile con un superviventia de duration normal.

Es describite le diagnose del defecto per arteriographia coronari. Experientias preliminari con le proponite tractamento chirurgic es presentate.

REFERENCES

1. Abrikossoff, A.: Aneurysma des linken Herzventrikels mit abnormer Abgangstelle der linken Koronararterie von der Pulmonalis bei einem funfmonatlichen Kinde. Virchow's Arch. Path. Anat. **203**: 413, 1911.
2. Kittle, C. F., Diehl, A. H., and Heilbrunn, A.: Anomalous left coronary artery arising from the pulmonary artery. J. Pediat. **47**: 198, 1955.
3. Kaunitz, P. E.: Origin of left coronary artery from pulmonary artery. Am. Heart J. **33**: 182. 1947.
4. Gasul, B. M., and Loeffler, E.: Anomalous origin of the left coronary artery from the pulmonary artery (Bland-White-Garland syndrome). Pediatrics **4**: 498, 1949.
5. Jurishica, A. J.: Anomalous left coronary artery. Adult type. Am. Heart J. **54**: 429, 1957.
6. Eidlow, S., and MacKenzie, E. R.: Anomalous origin of the left coronary artery from the pulmonary artery; report of a case diagnosed clinically and confirmed by necropsy. Am. Heart J. **32**: 243, 1946.
7. Sanes, S., and Kenny, F. E.: Anomalous origin of the left coronary artery from pulmonary artery. Am. J. Dis. Child. **48**: 113, 1934.
8. Soloff, L. A.: Anomalous coronary arteries arising from the pulmonary artery. Am. Heart J. **24**: 118, 1942.
9. Smith, J. C.: Review of single coronary artery with report of 2 cases. Circulation **1**: 1168, 1950.
10. Sarnoff, S. J., Case, R. B., Waithe, P. E., and Isaacs, J. P.: Insufficient coronary flow and myocardial failure as a complicating factor in hemorrhagic shock. Am. J. Physiol. **176**: 439, 1954.
11. Master, A. M., Dack, S., Horn, H., Freedman, B. I., and Field, L. E.: Acute coronary insufficiency due to acute hemorrhage; an analysis of 103 cases. Circulation **1**: 1302, 1950.
12. Case, R. B., Berglund, E., and Sarnoff, S. J.: Ventricular function. VII. Changes in coronary resistance and ventricular function resulting from acutely induced anemia and the effect thereon of coronary stenosis. Am. J. Med. **18**: 397, 1955.
13. Muller, W. H., Jr., and Dammann, J. F., Jr.: The treatment of certain congenital malformations of the heart by the creation of pulmonic stenosis to reduce pulmonary hypertension and excessive pulmonary blood flow. A preliminary report. Surg., Gynec. & Obst. **95**: 213, 1952.
14. Edwards, J. E.: Functional pathology of congenital cardiac disease. Pediat. Clin. North America. Feb. 1954, 13.
15. Brooks, H. St. J.: Two cases of an abnormal coronary artery of the heart arising from the pulmonary artery. J. Anat. Physiol. **20**: 26, 1886.
16. Sabiston, D. C.: Personal communication.
17. Morrow, A. G., Sanders, R. J., and Braunwald, E.: The nitrous oxide test. An improved method for the detection of left-to-right shunts. Circulation **17**: 284, 1958.
18. Apley, J., Horton, R. E., and Wilson, M. G.: The possible role of surgery in the treatment of anomalous left coronary artery. Thorax **12**: 28, 1957.

Clinical Observations with the Frank Precordial Lead System

By J. A. Abildskov, M.D., W. W. Street, M.D., N. Solomon, B.A., and A. H. Toomajian, B.A.

Several new lead systems for electrocardiography and vectorcardiography have been proposed. Clinical evaluation of these systems is necessary to determine whether they yield useful information in addition to that furnished by conventional leads and whether the same information obtained from conventional leads appears in recognizable form in the new leads. This study is a step toward such an evaluation of one of the proposed lead systems.

THERE has been considerable effort to devise more adequate systems of electrode placement than those currently employed in electrocardiography. It is well known that many assumptions inherent in representing the body as simple geometric figures are only approximations and it is possible that eliminating the necessity for such assumptions may increase the usefulness of records of the heart's electric activity. It is also possible that an improved electrode system will permit satisfactory examination of electric activity in the heart with fewer leads than are now used in clinical electrocardiography. Evaluation of these possibilities requires clinical studies employing newly proposed electrode arrangements. This evaluation will not be complete without study of vectorcardiograms in which projections of electric activity are combined synchronously but it also appears worthwhile to investigate electrocardiograms from the new electrode systems.[1] The latter studies may be expected to provide information concerning the form in which findings of known significance in conventional leads are reflected by the new systems. The present study was undertaken to obtain such information for the lead system proposed by Frank.[2]

From the Department of Medicine, State University of New York, Upstate Medical Center, Syracuse, N. Y.

This investigation was supported by a research grant (H-3241) from the National Heart Institute of the National Institutes of Health, U. S. Public Health Service and by a fellowship grant from the Heart Association of Onondaga County.

Materials and Methods

Ninety-one patients with normal electrocardiograms and 71 patients with a variety of etiologic types and electrocardiographic manifestations of heart disease were studied. Subjects with normal electrocardiograms were in the age range of 21 to 71 years and the patients with abnormal tracings varied in age between 29 and 78 years.

Electrocardiographic leads reflecting the horizontal (X), vertical (Y), and anteroposterior (Z) components of the heart's electric activity were recorded with the Frank electrode system. Electrodes were located on the neck, left leg, and thorax in the front and back midlines, right and left midaxillary lines, and at an angle of 45 degrees between the front midline and the left midaxillary line. All electrodes on the thorax were located at the level of the fifth intercostal space at the sternum. Resistor networks with components having the ratios recommended for this lead system and a range of values appropriate to the input impedance of the electrocardiograph were employed. The polarity of leads X and Y was comparable to leads I and aV_F with upward deflections in X representing vectors directed to the left and upward deflections in Y indicating vectors directed downward. In lead Z upward deflections represented vectors directed posteriorly. A conventional electrocardiogram including standard leads, augmented unipolar limb leads, and precordial leads V_1 through V_6 was recorded immediately before or after Frank system leads were obtained. Serial electrocardiograms were available for most of the patients with heart disease. All leads were recorded consecutively at a paper speed of 25 mm. per second with a conventional electrocardiograph.

The conventional leads and those obtained with the Frank system were inspected and described in terms commonly employed in electrocardiographic interpretation. Specific items of clinically useful information from the conventional tracings were listed and the presence or absence of each of these items in the Frank leads were noted. Lead X was examined for counterparts of information appearing in leads I, aV_L, aV_R, V_5 and V_6, and lead Y for the counterparts of data in leads II, III, and aV_F. Lead Z was examined for the counterparts of information in leads V_1 through V_6. When an item of information in conventional leads did not have a recognizable counterpart in 1 lead from the Frank system, the other 2 leads from this system were examined for evidence of this specific information. It was recognized that counterparts of findings from a certain conventional lead would not always appear in the same Frank system lead. If all clinically useful information in conventional leads was reflected by the Frank system, however, recognizable counterparts of this data would be expected in 1 or more of the 3 leads. To provide another comparison of conventional and Frank system leads the electric axis of the QRS was calculated from the algebraic sum of maximal upward and downward deflections in leads I and aV_F and from leads X and Y.

Results

P waves. In all normal records obtained with the Frank system, P waves were upright or isoelectric in leads X and Y. Normal P waves in lead Z were upright in 11 records, diphasic in 7, and inverted in the remaining 67 records.

Five conventional electrocardiograms had P waves that were abnormal on the basis of duration or amplitude. All these records were from patients with mitral valve disease and all had roentgenographic evidence of left atrial enlargement. In each case P waves in lead X were qualitatively similar to those in lead I and waves in Y were similar to those in aV_F. The polarity of P waves in the precordial leads of these subjects showed no consistent differences from that in normal records, but in lead Z of all of these records P waves were upright or diphasic with the major component upright. Since the majority of normal records showed inverted P waves in lead Z, these findings suggest that posteriorly directed vectors reflected by the Frank system may be helpful in recognizing left atrial enlargement. Study of a larger number of patients will be necessary to further evaluate this possibility.

QRS Complexes. The electric axis of the QRS calculated from leads I and aV_F of normal records had an average of 31° and a range of −13 to +82°. A similar quantity calculated from X and Y of the Frank system had a narrower range, from 0 to 67°, with an average of 33°. The range of electric axis in all abnormal records obtained with the Frank system was greater than in conventional leads. The axis calculated from leads X and Y had a range of −171° to +154°, with an average of 20°, and that calculated from leads I and aV_F had a range of −90 to +146, with an average of 25°.

The counterparts of most of the QRS abnormalities in conventional leads could be recognized in the Frank system leads. These findings cannot be quantitated, since the range of normal variations in leads obtained with the new system has not been established but the findings can be illustrated by selected examples. Figure 1*A* shows representative records from a normal subject for comparison with the abnormalities shown by other records in this and later figures. The records in figure 1*B* illustrate findings in patients with anterior and lateral myocardial infarction. The deep QS waves in V_1 through V_4 have their counterpart in lead Z, which does not show a Q wave. Normal Z leads always showed initial vectors directed anteriorly and represented by Q waves in lead Z. Nine records in this series showed evidence of old anterior infarction in the conventional electrocardiogram and 8 of these had no Q wave in the Z lead from the Frank system. One record from a patient with anterior infarction showed small Q waves in lead Z. The average amplitude of Q waves in lead Z in normal records was 0.25 mv. but the range was 0.05 to 0.75 and the small Q wave in the record of the patient with anterior infarction was comparable to the smaller ones present in some normal records. These findings seem to indicate that most, but not all, instances of anterior infarction recognizable in conventional pre-

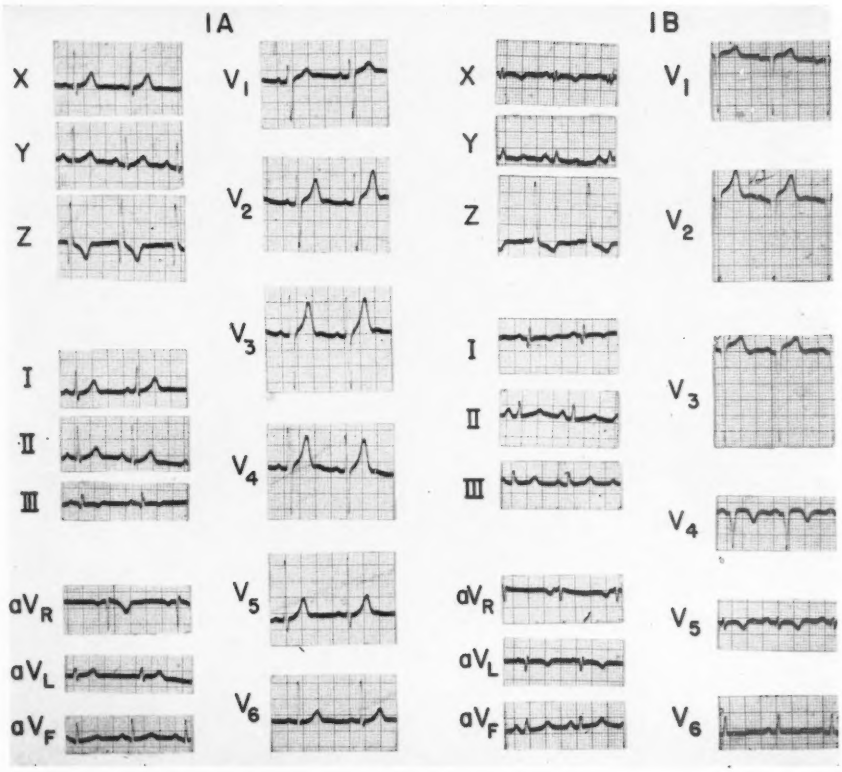


FIG. 1. *A*. Frank system leads, standard and unipolar limb and precordial leads from a normal subject. *B*. The same leads from a patient with anterolateral myocardial infarction. Q waves in leads I and aV_L have their counterpart in Q waves in lead X and Q waves in V_1 through V_4 have their counterpart in an R wave in lead Z indicating vectors directed posteriorly.

cordial leads will be manifest in the Frank leads by initial vectors directed posteriorly.

Four records in this series showed evidence of lateral wall infarction manifest by abnormal Q waves in leads I, aV_L and V_6. The X lead of 2 of these patients showed Q waves as illustrated by figure 1*B*. The records of the other 2 patients will be described in the section concerning QRS abnormalities in conventional tracings that did not have recognizable counterparts in the Frank leads.

Six records in this series showed evidence of old posterior wall infarction. All these records had Q waves in leads II, III, and aV_F and all showed similar Q waves in lead Y.

Two records in the series showed complete left bundle-branch block. In both records lead X had QRS complexes similar in form to those in lead I and complexes in aV_F were similar to those in Y. Lead Z showed initial Q waves and large R waves corresponding to R waves and deep S waves in leads V_1 through V_4. An example of these records is shown in figure 2*A*.

One conventional electrocardiogram showed complete right bundle-branch block. The Frank leads showed a wide S wave in lead X comparable to that in lead I and lead Z showed Q and R waves with a terminal S wave, which was not present in this lead in any normal records. This S wave appeared to be the counterpart of the large R′ wave in V_1 and V_2 of the conventional tracing. These records are shown in figure 2*B*.

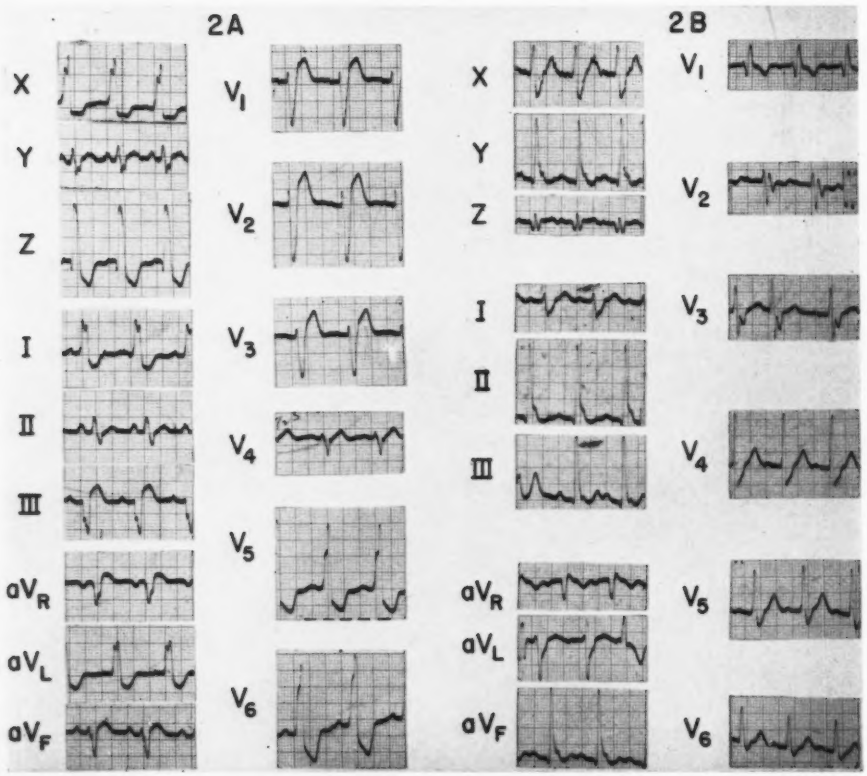


FIG. 2. *A*. Tracings from a patient with left bundle-branch block in which all significant features of the conventional leads have counterparts in the Frank system leads. *B*. Tracings from a patient with right bundle-branch block. In these records the wide S wave in leads I, aV_L, V_5, and V_6 is represented by a similar wave in lead X and the R′ wave in V_1 and V_2 has its counterpart in the terminal S wave in lead Z.

In 4 records there were QRS abnormalities in the conventional electrocardiogram, which did not appear to have recognizable counterparts in the Frank system leads. The records shown in figure 3 are examples of these findings. Figure 3*A* shows a conventional tracing with an R′ wave in V_1 and V_2, which was interpreted as indicative of incomplete right bundle-branch block. Lead Z from this patient shows Q and R waves similar to those in normal records but there is no evidence of late excitation directed anteriorly. One other record in this series showed comparable findings.

Figure 3*B* shows a conventional tracing with Q waves in leads I and aV_L. These waves were considered to be the result of lateral wall infarction, since earlier serial tracings had shown ST-segment and T-wave changes of the type associated with the evolution of recent infarction. Lead X from this subject did not show Q waves and leads Y and Z were not recognizably different from these leads in some normal records. One other record in which evidence of lateral infarction in the conventional tracing was not recognizable in the Frank leads was encountered in this series.

S-T Segments and T Waves. The 91 normal records obtained with the Frank system showed upright T waves in lead X. T waves in lead Y were upright in 88 records and iso-

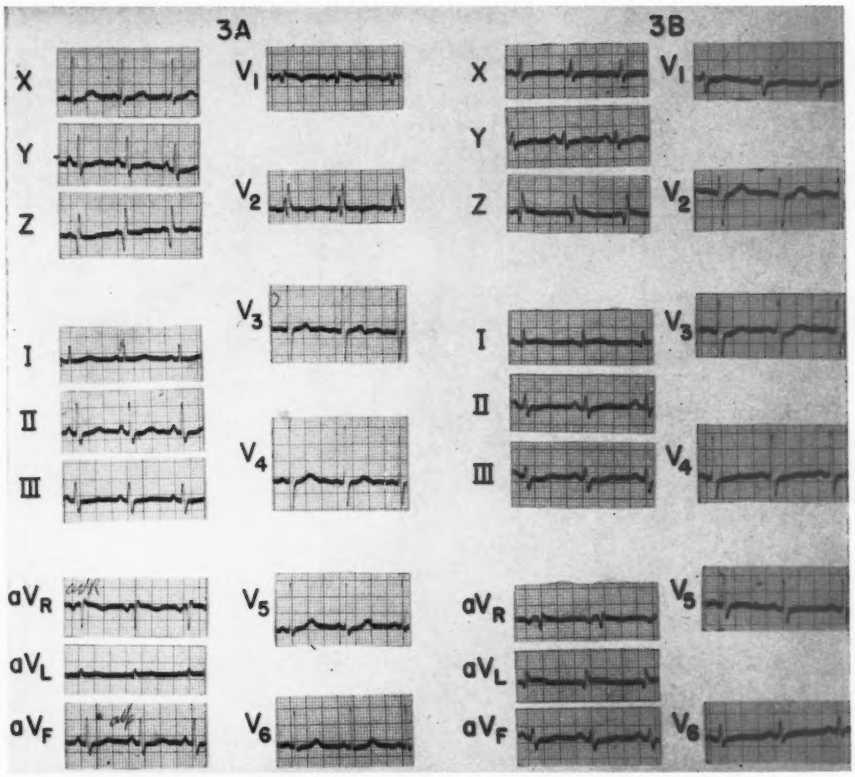


FIG. 3. *A*. Tracings in which an R′ wave is present in leads V_1 and V_2 and has no recognizable counterpart in the Frank system leads. *B*. Tracings in which small Q waves are present in leads I and aV_L. Earlier serial tracings on this patient had shown changes characteristic of recent lateral infarction. In the Frank system leads there was no recognizable counterpart of the Q waves in I and aV_L.

electric in the remaining 3. T waves in lead Z were inverted in 79, isoelectric in 9, and upright in 3 records. Among the 77 abnormal conventional electrocardiograms, 74 had significant ST-segment and T-wave abnormalities with easily recognizable counterparts in the Frank leads. These included displacement of the S-T segments and inversion or low voltage of T waves in leads I, aV_L, V_5, and V_6, which had their counterparts in lead X and similar findings in leads II, III, and aV_F with counterparts in lead Y. There were also records in which T-wave inversion in leads V_3 and V_4 had its counterpart in upright T waves in lead Z, since this lead showed inverted or diphasic waves in all but 3 normal records. An example of inverted T waves in anterior precordial leads reflected by upright T waves in Z is shown in figure 4*A*.

Seven conventional tracings had clinically significant T-wave findings without recognizable counterparts in the Frank system leads. These included the 3 normal records in which T waves were upright in lead Z and 4 records in which T-wave abnormalities in conventional leads were not recognizable in leads from the Frank system. Two of these records showed low or inverted T waves in V_1 through V_4 but T waves in lead Z were diphasic or inverted as in normal Z leads. One of these records is shown in figure 4*B*.

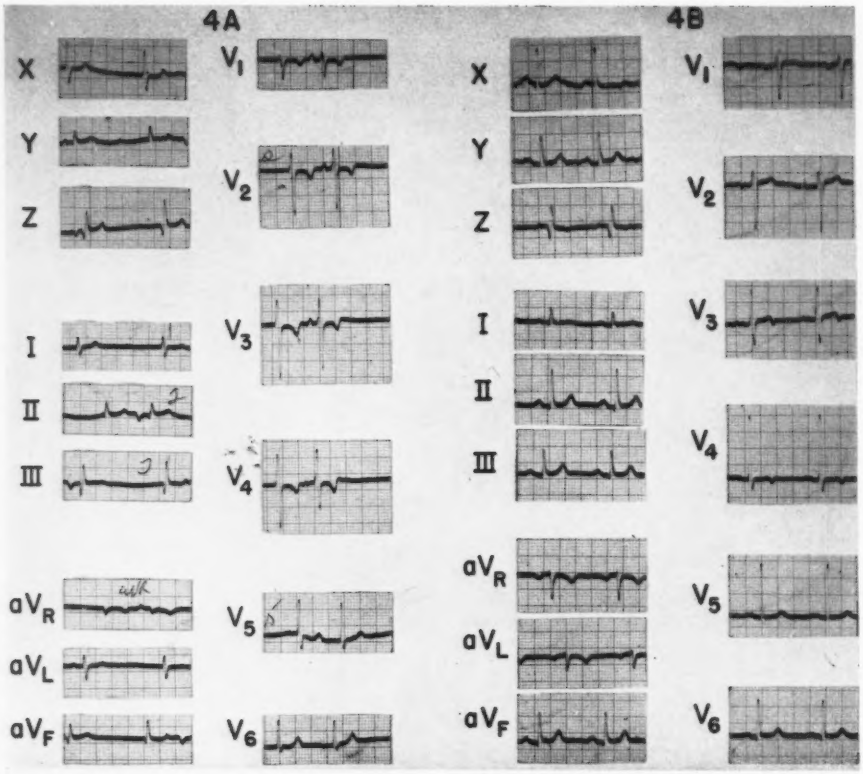


FIG. 4. *A*. Tracings in which T waves are inverted in V_1 through V_6. The counterpart of this finding is in lead Z which shows upright T waves. *B*. Tracings in which T waves are diphasic in leads V_3 and V_4. No counterpart of this finding could be recognized in Frank system leads.

Another record showed low voltage of T waves in leads I, aV_L, V_5, and V_6, while T waves in lead X were upright and had an amplitude comparable to that in most normal records. The other conventional tracing with significant T-wave findings that were not reflected in the Frank leads showed high peaked T waves in V_2 through V_4 suggestive of hyperkalemia. T waves in lead Z were inverted and had an amplitude comparable to that seen in many normal records.

DISCUSSION

The eventual purpose of new electrode systems is improvement in the detection of cardiac disease. In this study, most, but not all of the findings of known clinical significance in conventional leads appeared in recognizable form in the Frank system leads. Since the study concerned findings of demonstrated clinical importance that were obtained from leads now in common use, the failure of all these findings to be reflected by the new leads appears to be a serious shortcoming of the system.

It is still possible that the new lead system will provide information of clinical significance other than that now supplied by conventional leads. Evaluation of this possibility will require definition of the range of normal variation among records obtained with the Frank system. Correlation of presumed abnormal findings with the clinical course and autopsy findings in a large series of patients

will also be necessary. Although the present study was not primarily concerned with the possibility of information in addition to that furnished by conventional leads, it yielded 2 supporting findings. One was the finding that left atrial enlargement resulted in atrial excitation vectors directed posteriorly to a greater degree than in normal records. Since the polarity of P waves in the precordial leads of these patients showed no consistent differences from that in normal records, it is suggestive evidence that the Frank system leads may be helpful in recognizing left atrial enlargement. Another finding that supports the possibility that the Frank system may provide information other than that furnished by conventional leads was the narrower range of the QRS axis in normal records obtained with this system. A similar finding has been reported with a lead system based on the work of McFee and Johnston.[3] While not direct evidence, these findings are consistent with less distortion of the heart's electric field by these systems. Since the range of QRS axis in abnormal records was not narrowed by the Frank system, these findings support the possibility that this system may decrease the range of some normal variations without necessarily obscuring abnormalities.

It should be emphasized that the present study of consecutively recorded electrocardiographic leads with the Frank electrode system is not equivalent to study of vectorcardiograms. In the latter records, projections of electric activity are combined synchronously to give certain data that cannot be derived from conventional electrocardiograms. In the further evaluation of the Frank electrode system, studies of vectorcardiograms will be necessary.

Summary

Conventional 12-lead electrocardiograms and 3 leads from the electrode system devised by Frank were recorded on 91 subjects with normal conventional tracings and 77 patients with a variety of electrocardiographic abnormalities. Leads from the new electrode arrangement were examined for the counterparts of specific findings of known clinical significance in the conventional records. The majority but not all of these findings appeared in recognizable form in the Frank system leads. Since the study concerned findings of known significance, which were obtained from electrocardiographic leads now in common use, the failure of all of these findings to appear in the new leads appears to be a serious defect of the system.

Summario in Interlingua

Electrocardiogrammas a 12 derivationes conventional e a 3 derivationes ab le systema de electrodos disveloppate per Frank esseva obtenite ab 91 subjectos con normal registrationes conventional e ab 77 patientes con un varietate de anormalitates electrocardiographic. Registrationes obtenite secundo le nove arrangiamento de electrodos esseva scrutinate pro correspondentias a phenomenos de cognoscite signification clinic in le electrocardiogramma conventional. Le majoritate de iste phenomenos—ben que non omnes—esseva presente in forma recognoscibile in le registrationes obtenite secundo le systema de Frank. Viste que le studio se concerneva con phenomenos de signification establite in electrocardiogrammas per derivationes que es in uso commun al tempore presente, le facto que non omne ille phenomenos appareva in le registrationes effectuate per medio del nove derivationes indica un serie defecto del systema.

REFERENCES

1. Johnston, F. D.: Editorial: Reflections on electrocardiography. Circulation **15**: 801, 1957.
2. Frank, E.: An accurate clinically practical system for spatial vectorcardiography. Circulation **13**: 737, 1956.
3. Abildskov, J. A., and Pence, E. D.: A comparative study of spatial vectorcardiograms obtained with the equilateral tetrahedron and a "corrected" system of electrode placement. Circulation **13**: 263, 1956.

A Comparison of the Serum Lipids, Lipoproteins, Glycoproteins, Urinary 17-Ketosteroids, and Gonadotropins in Eunuchs and Control Male Subjects

By Robert H. Fukman, M.D., R. Palmer Howard, M.D., M. R. Shetlar, Ph.D., E. Corinne Keaty, Ph.D., and Richard Imagawa, M.D.

The proclivity of men to coronary artery disease has been recognized for almost 2 centuries. The gonadal hormones have understandably come under scrutiny in the search for the explanation of this marked sex difference in susceptibility to disease. Sex hormones are known to alter the physical state of the serum lipids. It has been suggested that eunuchs suffer a less severe form of coronary atherosclerosis than uncastrated subjects. This study compares the serum lipids and lipoproteins, as well as other serum and urinary constituents, in 24 castrated and 20 uncastrated institutionalized men.

THE concept of coronary atherosclerosis primarily as a disease of men had its origin almost 2 centuries ago[1] and appears to be one of the few points over which there is relatively little disagreement among students of atherosclerosis. Indirect support of this concept is provided by Wuest, Dry, and Edwards[2] and by Rivin and Dimitroff[3] whose studies indicated that castrated women suffer a more severe form of coronary atherosclerosis than uncastrated women. More directly applicable are the suggestions of White,[4] Howard and Gertler,[5] and Hawke[6] that eunuchs manifest less anatomic evidence of coronary atherosclerosis than uncastrated men. These differences may be related, at least in part, to the known influence of gonadal steroids on serum lipids and lipoproteins.[7] Considerations such as these prompted us to study a group of 24 eunuchs and 20 uncastrated men, all institutionalized at a training school for the mentally retarded.

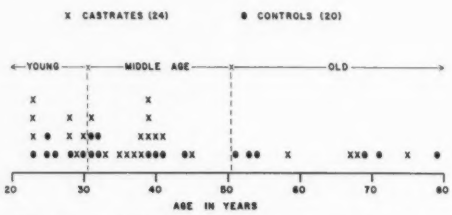


FIG. 1. Distribution of subjects according to age at the time of study.

Selection of Subjects and Methodology

Only subjects in apparent good health were retained in this study after physical examination, electrocardiogram, chest x-ray, and determinations of the serum total protein and hemoglobin had been made. There were no hypertensive individuals or members of the Hebrew race. There was 1 Negro among the eunuchs, none in the control group.

The age distribution for both groups was between 23 and 79 years and is shown in figure 1. The mean age of the eunuchs was 39, that of the controls 41. Castrated and control subjects were matched with respect to age and weight as closely as the nature of the school population would permit.

The mean body weight of the castrates was 69.5 ± 2.7 Kg., that of the controls 65.5 ± 2.3 Kg. Mean body surface area of the castrates was 1.80 ± .04 $M.^2$, that of the controls 1.72 ± .03 $M.^2$

From the Cardiovascular Section and the Endocrinology and Metabolism Section, Oklahoma Medical Research Foundation, the Departments of Medicine and Biochemistry, University of Oklahoma School of Medicine and the Research Laboratory, V. A. Hospital, Oklahoma City, Okla.

This study was supported in part by research grants from the National Heart Institute (H-1429 and H-1694) of the U. S. Public Health Service, the Oklahoma State Heart Association, The Smith, Kline and French Foundation, Philadelphia, Pa. and the Ayerst Laboratories, New York, N. Y.

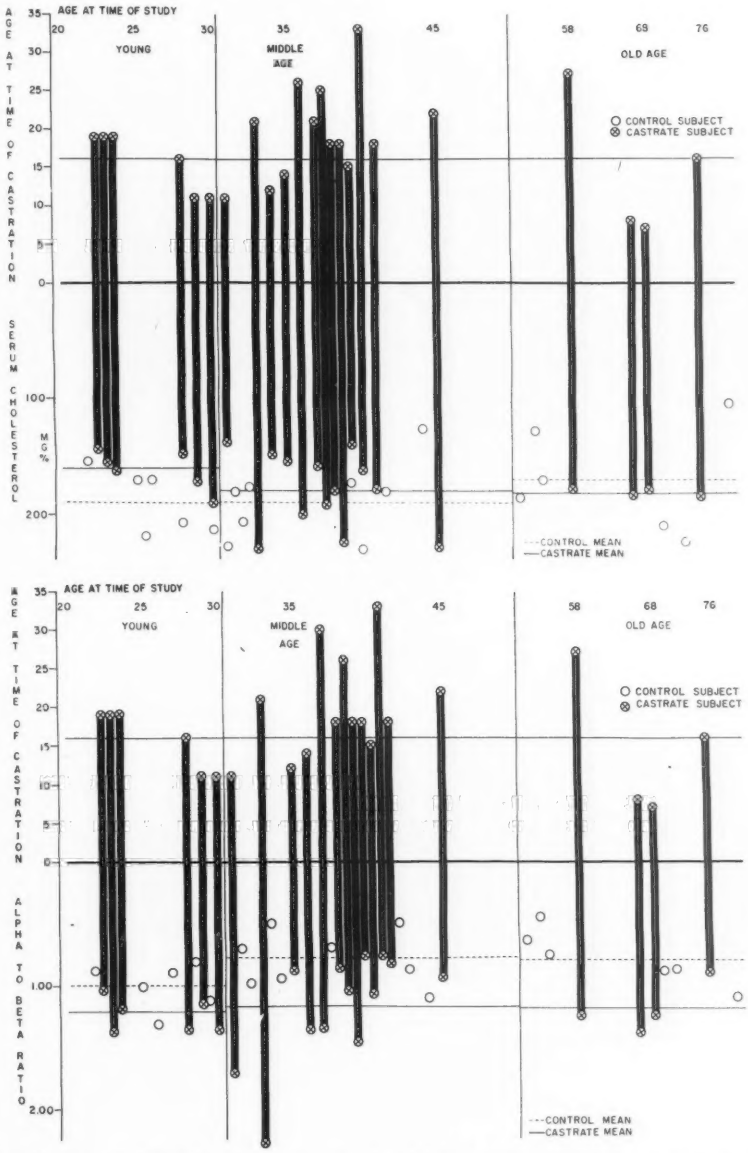


FIG. 2 *Top.* Relationship between age of subject at castration (*upper vertical axis*), mean serum cholesterol concentration (*lower vertical axis*), and age at time of study. Mean serum cholesterol values for castrates and controls are also indicated in each age category.

FIG. 3 *Bottom.* Bar graph depicting relationship between age of subject at castration (*upper vertical axis*), mean value of the high density/lower density or "alpha/beta" lipoprotein ratio (*lower vertical axis*) and age at time of study. Mean values of the ratios for castrates and controls are also indicated in each category.

The mean age at castration was 18 years. The relationship between age at castration and age at the time of this study is depicted in figure 2. It is of interest to note that castration had been accomplished by the sixteenth year in 10 subjects. One subject, age 28, was found on examination

TABLE 1.—*Serum Lipids and Lipoproteins; Mean Values* and Standard Errors*

Determination	Age	Castrates			Controls		
		Mean values	No. subjects	No. samples	Mean values	No. subjects	No. samples
Total cholesterol mg. %	21–30†	161 ± 6	7	32	189 ± 11	6	33
	31–50	180 ± 9	13	71	188 ± 12	8	23
	51 & over	182 ± 2	4	21	171 ± 17	6	14
	All ages	175 ± 6	24	124	183 ± 8	20	70
Phospholipid mg. %	21–30	226 ± 8	7	22	240 ± 12	6	24
	31–50	238 ± 8	13	49	245 ± 13	8	20
	51 & over	243 ± 3	4	13	248 ± 29	6	13
	All ages	235 ± 5	24	84	244 ± 10	20	57
Ratio: Cholesterol / Phospholipid	21–30	0.70 ± .03	7	22	0.78 ± .04	6	24
	31–50	0.72 ± .02	13	49	0.76 ± .02	8	20
	51 & over	0.77 ± .03	4	13	0.69 ± .03	6	13
	All ages	0.73 ± .01	24	84	0.75 ± .02	20	57
$-S_{1.21}$ 0–12 mg. % ("alpha") lipoproteins	21–30	207 ± 11	7	32	193 ± 32	6	33
	31–50	195 ± 10	13	71	171 ± 14	8	24
	51 & over	217 ± 4	4	22	188 ± 30	6	14
	All ages	202 ± 7	24	125	183 ± 14	20	71
$-S_{1.21}$ 25–40 mg. % ("beta") lipoproteins	21–30	173 ± 6	7	32	192 ± 18	6	31
	31–50	183 ± 14	13	61	235 ± 22	8	21
	51 & over	191 ± 16	4	21	232 ± 30	6	11
	All ages‡	182 ± 8	24	114	221 ± 14	20	63
$-S_{1.21}$ 25–70 mg. % ("beta") lipoproteins	21–30	203 ± 9	7	32	212 ± 16	6	31
	31–50	227 ± 13	13	61	271 ± 21	8	21
	51 & over	219 ± 17	4	21	285 ± 33	6	11
	All ages†	219 ± 8	24	114	257 ± 16	20	63
Ratio: $\frac{-S_{1.21}\ 0–12}{25–40}$ ("alpha"/"beta")	21–30	1.21 ± .05	7	32	1.00 ± .08	6	31
	31–50‡	1.17 ± .12	13	61	0.77 ± .08	8	21
	51 & over‡	1.19 ± .10	4	21	0.79 ± .09	6	11
	All ages§	1.18 ± .07	24	114	0.85 ± .05	20	63
Ratio: $\frac{-S_{1.21}\ 0–12}{\text{Total Cholesterol}}$	21–30	1.29 ± .05	7	32	1.01 ± .12	6	33
	31–50	1.12 ± .07	13	71	0.94 ± .09	8	23
	51 & over	1.21 ± .03	4	21	1.11 ± .13	6	14
	All ages†	1.18 ± .04	24	124	1.01 ± .06	20	70
Ratio: $\frac{-S_{1.21}\ 0–12}{\text{Phospholipid}}$	21–30	0.91 ± .04	7	22	0.79 ± .12	6	24
	31–50	0.81 ± .04	13	49	0.71 ± .06	8	20
	51 & over	0.93 ± .05	4	13	0.75 ± .06	6	13
	All ages†	0.86 ± .03	24	84	0.75 ± .05	20	57

* Values listed are "true means" where N = number of subjects (rather than number of samples) studied.

† Differences between castrates and controls in this group significant at 0.05 level.

‡ Differences between castrates and controls in this group significant at 0.02 level.

§ Differences between castrates and controls in this group significant at 0.001 level.

during the course of the study to be eunuchoidal but not castrate. There was a history of testicular atrophy early in childhood, the testes were extremely small, and the body build, fat, and hair distribution were definitely eunuchoidal. Because of these findings he was retained in the castrate group only for compilation of data presented in the tables.

Five blood samples were obtained from each eunuch (total number of samples 124) and 3 from each control subject (total number 70) in most instances. Blood was usually obtained at intervals of several months over a 2-year period. All blood was drawn in the postabsorptive state. Overnight urine specimens were collected whenever possible for determinations of 17-ketosteroid and urinary gonadotropin. Analyses were performed on a total of 49 urine specimens from 19 control subjects and 67 specimens from 24 castrates.

Lipoproteins were determined refractometrically after preparative ultracentrifugation at solvent density 1.21 Gm. per ml., according to the method of Lewis, Green, and Page[8] as employed in this laboratory.[7]

The value of the ratio $\frac{\text{high density } -S_{1.21}\ 0\text{-}12}{\text{lower density } -S_{1.21}\ 25\text{-}40}$ ("alpha") / ("beta") lipoproteins is employed to provide an index of the relative amounts of these 2 major lipoprotein groups. Use is also made of the values of the ratios $\frac{-S_{1.21}\ 0\text{-}12 \text{ lipoproteins}}{\text{total cholesterol}}$ and $\frac{-S_{1.21}\ 0\text{-}12 \text{ lipoproteins}}{\text{phospholipid}}$ to relate high density lipoprotein concentrations to the chemically determined native serum total cholesterol and phospholipid levels. Total and unesterified cholesterol were determined by the method of Sperry and Webb[9] and lipid phosphorus by a modification[10] of the method of Youngburg.[11] The factor 25 was used to convert lipid phosphorus to phospholipid.

Urinary gonadotropin was assayed according to the nondialysis method of Klinefelter, Albright, and Griswold,[12] and levels of less than 96 mouse uterine units per 24 hours were considered normal. Urinary neutral 17-ketosteroids were determined by the Zimmerman reaction. Initially, acid hydrolysis, extraction with carbon tetrachloride and a modified Zimmerman reaction were employed according to the technic outlined by Holtorff and Koch.[13] In analyses undertaken after May 1955, the technic proposed by Klendshoj, Feldstein, and Sprague[14] was employed, without change in values considered "normal."

Serum glycoprotein (protein-bound carbohydrate) according to the method of Shetlar, Foster, and Everett,[15] in which the results are expressed in terms of bound hexose, and total serum protein by the method of Weichselbaum[16] were determined in 27 samples of serum from 11 control subjects and in 63 samples from 22 castrates. The ratio $\frac{\text{serum glycoprotein hexose} \times 100}{\text{total protein}}$ is utilized to relate the concentration of protein-bound carbohydrate to the total concentration of circulating protein. The mean age of the controls whose sera were studied for glycoproteins was 36 years, that of the castrates 40.

The data for the 2 groups are compared according to the following age classifications: 21-30 ("young"), 31-50 ("middle-aged"), and over 50 years of age ("old"), as well as irrespective of age. The significance of differences was determined by t test.

Results

Mean values for the several lipid and lipoprotein fractions studied are presented in table 1.

Mean serum total cholesterol levels were significantly lower in the castrates only in the young or 21 to 30-year age group. The mean values for the 2 groups in the other age classifications were not significantly different. The degree of esterification was similar in all of the subjects.

Differences in serum phospholipid concentrations between eunuchs and controls were not significant at any age level, nor did cholesterol/phospholipid ratios differ significantly.

Higher concentrations of high density ($-S_{1.21}$ 0-12 or "alpha") lipoproteins characterized the castrate group at each age level as well as irrespective of age, although these differences were not statistically significant.

Lower concentrations of lower density ($-S_{1.21}$ 25-40 or "beta") lipoproteins characterized the castrate group at every age level, but statistically these differences were significant only when the castrate and control groups were considered in their entirety. The more inclusive $-S_{1.21}$ 25-70 lower density lipoprotein concentrations were also consistently lower in the castrates but, as was the case for the $-S_{1.21}$ 25-40 fraction, the difference was statistically significant only when the 2 groups were considered in their entirety.

TABLE 2.—*Glycoproteins; Mean Values* and Standard Errors, All Ages*

Determination	Castrates			Controls		
	Mean values	Subjects	Samples	Mean values	Subjects	Samples
Serum Glycoprotein hexose† mg. %	146±3	22	63	138±2	11	27
Serum total protein, Gm. %	7.27±.12	22	62	7.46±.09	11	27
Glycoprotein hexose×100† / Total protein	2.00±.05	22	62	1.85±.04	11	27

* Values listed are "true means" where N = number of subjects (rather than number of samples) studied.
† Differences between castrates and controls significant at 0.05 level.

TABLE 3.—*Ketosteroid Excretion; Mean Values* and Standard Errors*

Determination	Age	Castrates			Controls		
		Mean values	Subjects	Samples	Mean values	Subjects	Samples
17-ketosteroid excretion, mg./24 hours	21–30	9.4±1.7	7	19	12.0±1.5	6	19
	31–50	9.7±0.7	13	41	10.4±1.2	8	18
	51 & over	5.3±1.0	4	6	6.2±0.5	5	12
	All ages	8.9±0.7	24	66	9.7±0.9	19	49
17-ketosteroid excretion, mg./L.	21–30	6.4±1.7	7	19	8.1±1.4	6	19
	31–50	5.2±0.7	13	41	9.5±2.1	8	18
	51 & over	3.9±0.4	4	6	6.9±2.1	5	12
	All ages†	5.3±0.6	24	66	8.4±1.1	19	49

* Values listed are "true means" where N = number of subjects (rather than number of samples) studied.
† Difference between castrates and controls significant at 0.05 level.

Low density lipoproteins with flotation rate characteristics above $-S_{1.21}$ 70 were inconstantly present in small amounts and did not differ significantly in the 2 groups. Concentrations of $-S_{1.21}$ 20-25 ("alpha-2") lipoproteins likewise did not differ in the 2 groups.

The values for high density: lower density $\left(-S_{1.21}\ \frac{0\text{-}12}{25\text{-}40}\ \text{or}\ \frac{\text{"alpha"}}{\text{"beta"}}\right)$ lipoprotein ratios were consistently higher in the castrates for all age groups, and the difference between castrates and controls was statistically highly significant in the middle and old age groups, and for the groups considered in their entirety.

The $\frac{-S_{1.21}\ 0\text{-}12}{\text{total cholesterol}}$ and $\frac{-S_{1.21}\ 0\text{-}12}{\text{phospholipid}}$ ratios had consistently higher values for all ages in the castrate group, but the differences were statistically significant only when the groups were considered in their entirety.

Mean values of glycoprotein and total protein are listed in table 2. Serum glycoprotein concentrations were significantly higher in the castrate group as was the value for the ratio $\frac{\text{glycoprotein hexose} \times 100}{\text{total protein}}$. Serum glycoprotein levels in the control subjects were generally within "normal limits," as determined on a larger group of apparently healthy subjects by Shetlar, Foster, Kelly, and Everett.[17] No significant differences were noted with respect to total serum protein concentrations.

TABLE 4.—*Gonadotropin Excretion, All Ages*

Mouse uterine units	Castrates			Controls		
	Number subjects	%	Number samples	Number subjects	%	Number samples
>384	16	67	22	1	5	1
>192	22	92	46	3	16	4
> 96	23	96	60	5	26	11
< 96	1	4	7	14	74	33
Total	24	100	67	19	100	44

Urinary 17-ketosteroid and gonadotropin values are presented in tables 3 and 4. The 17-ketosteroid excretion per 24 hours did not differ significantly between the 2 groups for any age category. When the urinary 17-ketosteroid concentration was determined, a significantly higher level was noted in the total control group. Urinary gonadotropin excretion was as expected, with the majority of eunuchs (22 out of 24) excreting more than 192 mouse uterine units per day while only 3 of 19 control subjects excreted more than 192 units.

DISCUSSION

The relatively small size of the samples of this unique population that were available for study limits the degree of statistical significance that can be assigned to many of the observed differences. Outstanding among the data for the castrates, however, are the consistently higher mean values for high density lipoprotein concentrations and the consistently lower mean concentrations of the lower density lipoproteins. There were no exceptions with respect to these mean values (table 1). The likelihood that such consistency was due to chance alone is extremely small ($1:2^{12}$). The value for the ratio of high density/lower density lipoprotein is, by virtue of its derivation, higher in the castrate group. Further emphasis is lent this consistency of difference in lipoprotein concentrations (and ratios) between the 2 groups by the fact that other than for the significantly lower native serum total cholesterol levels in the young castrates, neither serum cholesterol nor phospholipid values differed significantly or consistently.

The differences between eunuchs and uncastrated men with respect to the high and lower density lipoproteins are characteristic of the changes observed when androgens are withdrawn from, or estrogens administered to, other subjects.[7]

The significantly lower serum cholesterol levels in the young castrates prompted further scrutiny of the data with reference to what influence the subject's age at the time of castration might have on his lipids and lipoproteins at the time of study. Figures 2 and 3 are of interest in this regard. It may be noted (fig. 2) that none of the young castrates had a serum cholesterol level in excess of the control mean serum cholesterol level. A young age at castration is of course inherent in the young castrate group. When the middle and old age groups are examined, it is of further interest to note that while none of the eunuchs who was subject to castration before the seventeenth year of age had a serum cholesterol value in excess of the mean serum cholesterol value, each of the 4 prepuberal castrates in the middle age group had individual mean serum cholesterol values (137 ± 6, 149 ± 10, 156 ± 3, and 141 ± 14 mg. per cent) statistically significantly lower ($p < 0.01$, $p < 0.05$, $p < 0.05$, $p < 0.05$) than the mean cholesterol level (180 ± 9 mg. per cent) for the middle age castrate group as a whole. There are, of course, some eunuchs in the middle age group who underwent castration later than the sixteenth year of age whose serum cholesterol values were also less than the mean control value.

Figure 3 denotes a somewhat different relationship among the 3 variables: age at castration, age at time of study, and the value for the ratio high density/lower density lipoproteins. It is noted that none of the values of this ratio in the castrate group was less than the mean control value, irrespective of age at castration or age at the time of study. It is also of interest to note that only 1 control subject, who happened to fall in the young age group, had a value for the high

density/lower density lipoprotein ratio that exceeded the mean value of this ratio in the eunuchs.

These observations suggest that the influence of the male gonad on the relative amounts of high and lower density serum lipoproteins is at least partially independent of age factors, e.g., the age at which gonadal influence is removed (at least up to the age of 33 years), and probably the age of the subject at the time serum lipoprotein relationships are determined, although the data suggest that alterations in lipoprotein relationships induced by gonadectomy are apt to be more striking in middle-aged male subjects. The influence of castration before the seventeenth year of age on the level of chemically determined serum cholesterol also appears to be somewhat independent of age, since the lower level characteristic of the young castrates was noted in the middle age group only in those subjects who were prepuberal castrates.

These data, then, are consistent with the hypothesis that the effect of withdrawal of gonadal hormones on the relative amounts of the 2 major serum lipoprotein fractions in men is at least partially independent of age, while the effect on the cholesterol concentration is maintained only when the gonads are removed at or before puberty.

The lack of significant differences in serum phospholipid levels in the 2 groups, previously noted by Hamilton, Bunch, Mestler and Imagawa,[18] is undoubtedly related to the fact that the lipid phosphorus content of the high and lower density lipoproteins is similar, namely 26.5 and 23.4 per cent respectively, as reported by Bragdon, Havel, and Boyle.[19]

The lack of significant differences between the eunuchs and uncastrated men with respect to low density lipoproteins of flotation rates in excess of $-S_{1.21}$ 70 (S_f 20) tends to minimize the etiologic or predictive significance of these low density lipoproteins in atherosclerosis (assuming that eunuchs suffer less atherosclerosis than uncastrated men).

The lower levels of urinary 17-ketosteroids in the eunuchs are obviously a consequence of castration, although the difference in 17-ketosteroid excretion between the 2 groups is quantitatively slight, presumably because of increased adrenal androgen synthesis in the eunuch. Qualitatively these adrenal androgens differ from those of gonadal origin inasmuch as they do not prevent the appearance of eunuchoidal somatic characteristics in the prepubescent castrate. The difference in the lipoprotein relationships of the 2 groups demonstrated in this study is an additional manifestation of this qualitative difference between testicular and adrenal androgens. No correlation was noted between urinary 17-ketosteroid excretion and a subject's age at castration, the concentration of high or low density lipoproteins or their ratio. Aging appeared to be associated with diminishing urinary 17-ketosteroids, a phenomenon previously described by Venning and Kazmin.[20]

A greater excretion of gonadotropins in castrated than in uncastrated subjects, is of course, expected. The reasons for elevated gonadotropin excretion in 3 of the control subjects are not apparent, since testicular size and consisteney were normal in each subject and there were no other stigmata of eunuchoidism or general systemic disease. Two of them were 53 and 79 years old and thus may have been examples of testicular tubular failure occurring with advancing years. When all data from these 3 subjects were excluded, no significant alteration of any of the mean values in the control group resulted.

Scrutiny of the lipid data for intragroup differences related to age reveals a significant ($p < 0.05$) increase in lower density $-S_{1.21}$ 25-70 lipoprotein concentrations in the control subjects on going from the young to the middle age group. This is in keeping with the observation of Jones et al.[21] that greater concentrations of S_f 12-20 ($-S_{1.21}$ 25-40) lipoproteins are noted in men beginning with the third decade of life. The failure of serum cholesterol to increase along with the lower density lipoproteins in this respect is attributable to the reduction in high density lipoprotein levels, which reduction, although

not statistically significant, nevertheless was of sufficient mean magnitude to obviate change in the mean cholesterol concentration on going from the young to middle age control group.

The increase in serum cholesterol levels noted in the eunuchs on going from the young to the middle age group is significant ($p < 0.01$) and resembles the increase reported to occur in women from age 33 through 58.[22]

The meaning of the glycoprotein and glycoprotein/total protein differences must await further study. At the present time all that can be said is that castrated subjects have higher serum glycoprotein concentrations than uncastrated subjects, absolutely as well as relative to the total serum protein concentration.

Finally the question of the possible relationship of these findings to the suggestion that the castrate enjoys a relative freedom from coronary atherosclerosis must be considered. It is tempting to suggest that the relatively greater concentrations of high density $-S_{1.21}$ 0-12 lipoproteins noted in the castrated group may be importantly related to this phenomenon. Such thinking gains support from the studies of Jencks and coworkers,[23] who demonstrated reduced concentrations of high density "alpha" lipoproteins and increased concentrations of lower density "beta" lipoproteins in men with a history of myocardial infarction. The predictive significance (and, therefore, possibly the etiologic significance) of the lower density S_f 12-20 and 20-100 lipoprotein concentrations in coronary atherosclerosis is certainly in doubt at present.[24]

While the correlation between the lipoprotein spectrum (considered in its entirety) and coronary atherosclerosis is receiving increasing support as a result of studies such as these, the establishment of such a correlation of course does not provide proof of etiologic relationship. Further work along these lines is clearly necessary.

The only other significant and sustained alteration in serum constituents reported to follow castration in the young adult male is a rise of 1 to 1.5 mg. in serum inorganic phosphate.[18] The meaning of this rise with respect to atherogenesis remains conjectural at this point.

The possibility must not be overlooked that personality changes resulting from castration are important, as well as the lipid changes. Increased tractability, stability, diminished aggressiveness, and, in general, a more tranquil existence usually follow castration in the human subject.[6] These characteristics tend to be associated in the minds of clinicians with relative freedom from disorders attributable to "stress," and with longevity and health.

Summary

Eunuchs and uncastrated male subjects are compared with respect to serum lipids, lipoproteins and glycoproteins, and with respect to the urinary excretion of gonadotropins and 17-ketosteroids.

The mean high density $-S_{1.21}$ 0-12 ("alpha") lipoprotein concentrations were consistently higher, and the lower density $-S_{1.21}$ 25-40 or 25-70 ("beta") lipoprotein concentrations consistently lower, in eunuchs than in uncastrated controls, irrespective of age at the time of study or time of castration. The ratio of "alpha" to "beta" lipoproteins was also consistently higher in eunuchs. These differences are characteristic of androgen withdrawal or estrogen administration.

The mean serum cholesterol level was significantly lower in the young eunuchs than in young controls. Lower individual serum cholesterol values in the middle aged eunuchs were noted only in those who had undergone gonadectomy prior to the seventeenth year of age. Mean serum cholesterol levels of the middle and old age castrated subjects and controls did not differ significantly.

The mean serum glycoprotein concentration was higher in eunuchs than in the controls. This was also true for the ratio $\frac{\text{glycoprotein hexose} \times 100}{\text{total protein}}$.

Urinary gonadotropin excretion was in excess of 192 mouse uterine units per day in 22 of 24 eunuchs, while only 3 of 19 control

subjects excreted more than 192 units per day.

Urinary 17-ketosteroid excretion per day did not differ significantly between the 2 groups. However, the urinary 17-ketosteroid concentration was significantly higher in the controls.

ACKNOWLEDGMENT

The authors wish to express their sincere thanks to Col. John B. Smith, Superintendent of the Winfield State Training School, Winfield, Kan., for permission to study these subjects, and to Dr. Harold H. Jones, Dr. Franklin R. Miller, Leitha Bunch, M.A., and other members of the Training School Staff at Winfield for much valuable assistance.

Acknowledgment is gratefully made of the technical assistance provided by Jane B. Faulkner, M.S., Alice W. Fryer, B.S., Betty S. Wamack, B.S., Emma Lou McDearmon, B.S., Marian MacAulay, Helen M. Hoffman, B.S., and Ilse M. Neeland. We wish also to express our thanks to Dr. Carl R. Doering, Professor of Preventive Medicine and Public Health, University of Oklahoma School of Medicine, and to Joanna Peter, B.S., for statistical analyses of the major portion of the data.

SUMMARIO IN INTERLINGUA

Eunuchos e non-castrate subjectos maseule es comparate con respecto al lipidos, lipoproteinas, e glycoproteinas del sero e al excretion urinari de gonadotropinas e 17-cetosteroides.

Le concentrationes medie del lipoproteinas a alte densitate $-S_{1.21}$ 0-12 (''alpha'') esseva regularmente plus alte e le concentrationes medie del lipoproteinas a plus basse densitates $-S_{1.21}$ 25-50 o 25-70 (''beta'') esseva regularmente plus basse in eunuchos que in le non-castrate subjectos de controlo, sin regardo al etate del individuos al tempore del studio o al tempore del castration. Le proportion de lipoproteinas ''alpha'' a lipoproteinas ''beta'' esseva etiam regularmente plus alte in eunuchos. Iste differentias es characteristic effectos del abstention de androgeno o del administration de estrogeno.

Le nivello medie del cholesterol in le sero esseva significativemente plus basse in juvene eunuchos que in juvene subjectos de controlo. Casos individual de reducite valores del cholesterol seral in eunuchos de etates intermediari occurreva solmente quando le gonadectomia habeva essite effectuate ante le etate de 17 annos. Le nivellos medie del cholesterol seral in castratos de etates intermediari e avantiate non differeva significativemente.

Le concentration medie del glycoproteina seral esseva plus elevate in eunuchos que in le subjectos de controlo. Le mesmo valeva pro le proportion $\frac{\text{glycoproteina}}{\text{proteina total}} = \frac{\text{hexosa}}{\text{proteina total}} \times 100$.

Le excretion urinari de gonadotropina esseva plus que 192 unitates myo-uterin per die in 22 ex 24 eunuchos e in solmente 3 ex 19 subjectos de controlo.

Le excretion urinari de 17-cetosteroides in 24 horas non differeva significativemente inter le duo gruppos. Tamen le concentration del 17-cetosteroides urinari esseva significativemente plus alte in le subjectos de controlo.

REFERENCES

1. HEBERDEN, W.: "Commentaries on the History and Cure of Diseases" published posthumously in London, 1802; taken from "Cardiac Classics" by F. A. Willius and T. E. Keys. St. Louis, the C. V. Mosby Company, 1941.
2. WUEST, J. H., DRY, T. J., AND EDWARDS, J. E.: The degree of coronary atherosclerosis in bilaterally oophorectomized women. Circulation **7**: 801, 1953.
3. RIVIN, A. U., AND DIMITROFF, S. P.: The incidence and severity of atherosclerosis in estrogen-treated males and in females with a hypoestrogenic or hyperestrogenic state. Circulation **9**: 533, 1954.
4. WHITE, P. D., Discussion of paper by BARR, D. P., RUSS, E. M., AND EDER, H. S.: Influence of estrogens on lipoprotein in atherosclerosis. Tr. A. Am. Physicians **65**: 102, 1952.
5. HOWARD, R. R., AND GERTLER, M. M.: Ketosteroids in coronary heart disease. J. Kansas M. Soc. **54**: 319, 1953.
6. HAWKE, C. C.: Castration and sex crimes. J. Kansas M. Soc. **51**: 470, 1950.
7. FURMAN, R. H., HOWARD, R. P., NORCIA, L. N., AND KEATY, E. C.: Influence of androgens and estrogens and related steroids on serum lipids and lipoproteins in hypogonadal and normal subjects. Am. J. Med. **24**: 80, 1958.
8. LEWIS, L. A., GREEN, A. A., AND PAGE, I. H.: The alpha and beta lipoprotein pattern of

normal and pathological human sera. Fed. Proc. **10**: 84, 1951.

9. Sperry, W. M., and Webb, M.: A revision of the Schoenheimer-Sperry method for cholesterol determination. J. Biol. Chem. **187**: 97, 1950.
10. Hawk, P. B., Oser, B. L., and Summerson, W. H.: Practical Physiological Chemistry. Ed. 12. Philadelphia, Blakiston Co., 1947, p. 541.
11. Youngburg, G. E., and Youngburg, M. V.: Phosphorus metabolism. I. A system of blood phosphorus analysis. J. Lab. & Clin. Med. **16**: 158, 1930.
12. Klinefelter, H. F., Jr., Albright, F., and Griswold, G. C.: Experience with a quantitative test for normal or decreased amounts of follicle stimulating hormone in the urine in endocrinological diagnosis. J. Clin. Endocrinol. **3**: 529, 1943.
13. Holtorff, A. F., and Koch, C.: The colorimetric estimation of 17-ketosteroids and their application to urine extracts. J. Biol. Chem. **135**: 377, 1940.
14. Klendshoj, N. C., Feldstein, M., and Sprague, A.: Determination of 17-ketosteroids in urine. J. Clin. Endocrinol. & Metab. **13**: 922, 1953.
15. Shetlar, M. R., Foster, J. V., and Everett, M. R.: Determination of serum polysaccharides by the tryptophan reaction. Proc. Soc. Exper. Biol. & Med. **67**: 125, 1948.
16. Weichselbaum, T. E.: An accurate and rapid method for the determination of proteins in small amounts of blood, serum and plasma. Am. J. Clin. Path. (Tech. Section) **10**: 40, 1946.
17. Shetlar, M. R., Foster, J. V., Kelly, K. H., and Everett, M. R.: Serum polysaccharide level in the normal state. Proc. Soc. Exper. Biol. & Med. **69**: 507, 1948.
18. Hamilton, J. B., Bunch, L. D., Mestler, G. E. and Imagawa, R.: Effect of orchiectomy upon chemical constituents of blood in young mature males, with special reference to sustained increase in the level of serum inorganic phosphorus. J. Clin. Endocrinol. & Metab. **16**: 301, 1956.
19. Bragdon, J. H., Havel, R. J., and Boyle, E.: Human serum lipoproteins. I. Chemical composition of four fractions. J. Lab. & Clin. Med. **48**: 36, 1956.
20. Venning, E. H., and Kazmin, V.: Excretion of urinary corticoids and 17-ketosteroids in the normal individual. Endocrinology **39**: 131, 1946.
21. Jones, H., Gofman, J., Lindrgen, F., Lyon, T., Graham, D., Strisower, B., and Nichols, A. V.: Lipoproteins in atherosclerosis. Am. J. Med. **11**: 358, 1951.
22. Adlersberg, D., Schaefer, L. E., Steinberg, A. G., and Wang, C.: Age, sex, serum lipids and coronary atherosclerosis. J.A. M.A. **162**; 619, 1956.
23. Jencks, W. P., Hyatt, M. R., Jetton, M. R., Mattingly, T. W., and Durrum, E. L.: A study of serum lipoproteins in normal and atherosclerotic patients by paper electrophoretic techniques. J. Clin. Invest. **35**: 980, 1956.
24. Gofman, J. W., Hanig, M., Jones, H. B.: Lauffer, M. A., Lawry, E. Y., Lewis, L. A., Mann, G. V., Moore, F. E., Olmsted, F., Yeager, J. F., Andrus, E. C., Barach, J. H., Beams, J. W., Fertig, J. W., Page, I. H., Shannon, J. A., Stare, F. J., and White, P. D.: Evaluation of serum lipoprotein and cholesterol measurements as predictors of clinical complications of atherosclerosis. Report of a cooperative study of lipoproteins and atherosclerosis. Circulation **14**: 691, 1956.

Nonpenetrating Traumatic Injury of the Aorta

By Loren F. Parmley, Lt. Colonel, MC, Thomas W. Mattingly, Brig. Gen., MC, William C. Manion, M.D., and Edward J. Jahnke, Jr., Maj., MC

Rupture or laceration of the aorta is a more common result of nonpenetrating traumatic injury than is generally appreciated. Approximately 15 per cent of individuals with traumatic rupture survive temporarily. If the lesion is promptly diagnosed appropriate surgical treatment may be life-saving. Diagnosis may be difficult and at times the rupture may remain clinically silent for variable periods. The natural course from aortic rupture to false aneurysm formation with secondary rupture of the aneurysm may be brief or extend over many years. Surgical treatment of a false aneurysm that has remained stable for a prolonged period has been successful, but in some instances conservative management may be the treatment of choice.

OF ALL the cardiovascular lesions that result from nonpenetrating traumatic injury none demonstrates the need for prompt recognition and surgical therapy as emphatically as rupture of the aorta that is not immediately fatal. That anyone survives complete transection of this major artery is almost unbelievable; nonetheless, an appreciable number have survived.

The medical literature contains many case reports of aortic rupture caused by trauma. According to Sailer[1] one of the first cases of aortic aneurysm, presumably the result of trauma, was reported in 1557 by Vesalius. Two of the larger series were reported by Kuhn,[2] who collected 75 cases published between 1895 and 1925, and Strassmann,[3] who reviewed the literature in 1947 in connection with his report on 72 cases of his own. Patients who have survived aortic rupture, including those in whom post-traumatic aortic aneurysms developed, have been less frequently reported. The English literature lists at least 57 cases[2-36] of aortic rupture caused by nonpenetrating trauma which the patients have survived for varying lengths of time. The lesion in all these cases was confirmed by postmortem or surgical examination. Other cases of aortic rupture with survival have been reported, but the diagnoses were made clinically. The 5 cases of traumatic aortic aneurysm recently reported by Steinberg[36] are well documented despite lack of surgical or postmortem confirmation in 4. Although an individual with an apparent traumatic aneurysm of the abdominal aorta has been reported to have survived 27 years after injury,[10] the relationship to trauma in this case may be questioned. However, the 27-year survival of an individual with a traumatic aneurysm of the thoracic aorta was also reported by Steinberg,[36] and 4 others in his series had survived for periods of from 2 to 21 years. One patient with a traumatic aneurysm of the thoracic aorta survived 8 years before surgical repair,[23] but most patients have lived for periods of from 15 minutes to 3 weeks before surgical intervention or death.

It is the purpose of this paper to present the salient clinical and pathologic features observed in our series of 296 cases of aortic injury caused by nonpenetrating trauma and to discuss the diagnosis and management of aortic rupture in those who survive the immediate effects of the injury. Of the 1,174 necropsy cases of traumatic injury of the heart and aorta we have studied from the files of the Armed Forces Institute of Pathology, 275 were cases of aortic rupture, 104 combined with cardiac injury (table 1). Included in the series are 2 living patients in whom traumatic aortic aneurysm has been corrected surgically. In addition to the 275 cases of aortic rupture, 21 cases of laceration

From the Armed Forces Institute of Pathology, and the Walter Reed Army Hospital, Washington, D. C.

involving only 1 or 2 layers of the aorta were studied, for a total of 296. In all but 1 of the 21 there was associated cardiac injury. Thirty-eight of the patients with aortic rupture survived the injury for a time.

Injuries other than cardiovascular were frequently sufficient to cause death. In an analysis of the cause of death in this series it was found that approximately 80 per cent of patients with combined cardiac and aortic injury and at least half of those with aortic rupture only would have died from their other injuries had there been no cardiovascular lesion.

The majority of patients were young men, only 4 of the 275 being women. This distribution does not reflect a true sex incidence, but only the sex distribution of the material at the Armed Forces Institute of Pathology, which is drawn from a predominantly male population. The average age in this series was 27 years, 18 and 85 years being the extremes.

The forces that produce aortic rupture are the same as for other nonpenetrating cardiovascular injuries; namely, direct and indirect forces, deceleration, compression, and blast. Often a combination of 2 or more of these forces is responsible.

The mechanism whereby aortic injury or rupture is produced varies with the type of force. A direct force that results in fracture or displacement of one of the dorsolumbar vertebrae may cause rupture of the aorta by shearing action.

Indirect force apparently acts through production of increased intravascular pressure. It has been demonstrated experimentally[37] that such a pressure may exceed 1,000 mm. Hg without causing rupture. An apparently normal human aorta has been ruptured by an aortic pressure of 2,070 mm. Hg.[38] Zehnder[29] tested the tensile strength of strips of aorta and calculated that pressure sufficient to cause rupture is equivalent to an intravascular pressure of 2,500 mm. Hg. Our series includes an instance of rupture of the arch of the aorta by indirect force resulting from a cave-in accident that suddenly covered the body with earth to the level of the midthorax. It is postulated that the volume of blood suddenly trapped in the aorta or forced into the aorta at the time of systole was sufficient to produce the extremely high pressure required to cause rupture.

TABLE 1.—*Sites of Rupture of the Aorta due to Nonpenetrating Trauma Tabulated to Show the Incidence of Rupture of a Specific Site and the Frequency of Associated Cardiac Injury in 275 Individuals*

Site of rupture	Isolated aortic rupture	Combined with cardiac injury	Total
Ascending aorta	17	47	64
Arch	16	6	22
Isthmus	95	29	124
Thoracic aorta	27	8	35
Abdominal aorta	11	2	13
Multiple sites	5	12	17
Totals	171	104	275

The most common cause of traumatic aortic rupture is the force generated by rapid deceleration of the body in either the vertical or horizontal plane. Hass[39] has pointed out that deceleration sets up differential forces between the various organs and tissues of the body, depending on their structure, location and attachments, and the direction of deceleration. Regions subjected to the greatest strain are at the points of junction of these differentially decelerated tissues. In the aorta the greatest strains are put upon the isthmus, where the relatively mobile thoracic aorta joins the fixed arch of the aorta, and on the ascending aorta, which joins the arch and the easily displaceable heart. Substantiation for this concept was provided by our series for the most frequent sites of rupture were at these 2 locations (table 1), the isthmus being the more vulnerable. Attention has also recently been drawn to a "whiplash" mechanism as a factor in producing aortic rupture.[29]

Usually a combination of forces is required to produce rupture. Zehnder's[29] calculations have raised reasonable doubt that the usual deceleration force encountered in

TABLE 2.—*Types of Accidents in which Nonpenetrating Trauma Produced Aortic Rupture or Rupture Associated with Cardiac Injury, in 275 Individuals*

Cause	Isolated aortic rupture	Combined with cardiac injury	Total
Automobile	114	42	156
Airplane	12	31	43
Vehicle vs pedestrian	9	7	16
Fall (long distance)	12	12	24
Motorcycle	3	1	4
Automobile vs train	0	2	2
Compression by heavy object	4	0	4
Buried by dirt	1	0	1
Direct blow by object	5	0	5
Unknown	11	9	20
Totals	171	104	275

automobile accidents could in itself produce aortic rupture. Table 2 lists the kinds of accidents in which individuals with aortic rupture were involved. The great majority were automobile accidents, where many factors may operate to produce aortic rupture.

PATHOLOGY

This study is based for the most part on autopsy material, the lesions of the aorta either being lethal or associated with other injuries that caused death. Most of the aortic lesions were ruptures, varying in length from a millimeter to complete transection, the majority being either complete or so extensive as to be classed as transections, since only a centimeter or so of the circumference of the aortic wall remained intact (fig. 1). No particular site in the circumference of the aorta seemed to be predisposed to rupture. In the majority it appeared as if rupture were spontaneous and simultaneous throughout the vessel wall. Ruptures involving only part of the aortic circumference were often posterior. Although partial ruptures of this type have been cited as the precursor of aneurysm formation, this development was equally frequent in those of our series who had complete

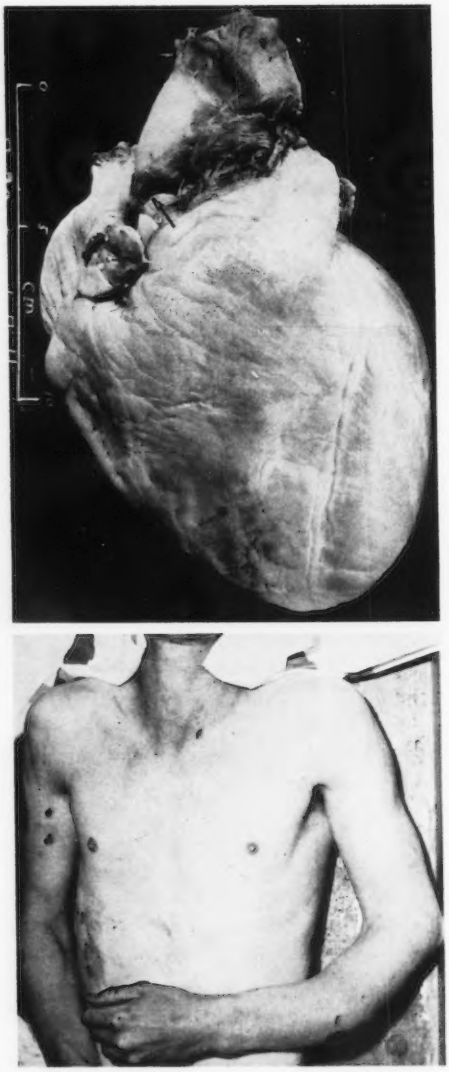


FIG. 1. (AFIP Acc. 571821). A 24-year-old white man killed in an automobile accident. *Top, A.* The gross specimen of the heart and great vessels reveals a Y-shaped laceration almost completely transecting the aorta 1 cm. above the aortic valve (*arrow*) and a 3-cm. transverse rupture of the right atrium. *Bottom, B.* The external appearance of the chest revealed minimal evidence of chest trauma.

transections. Occasionally, ragged, spiral, or longitudinal ruptures occurred, but in the majority the rupture was transverse and

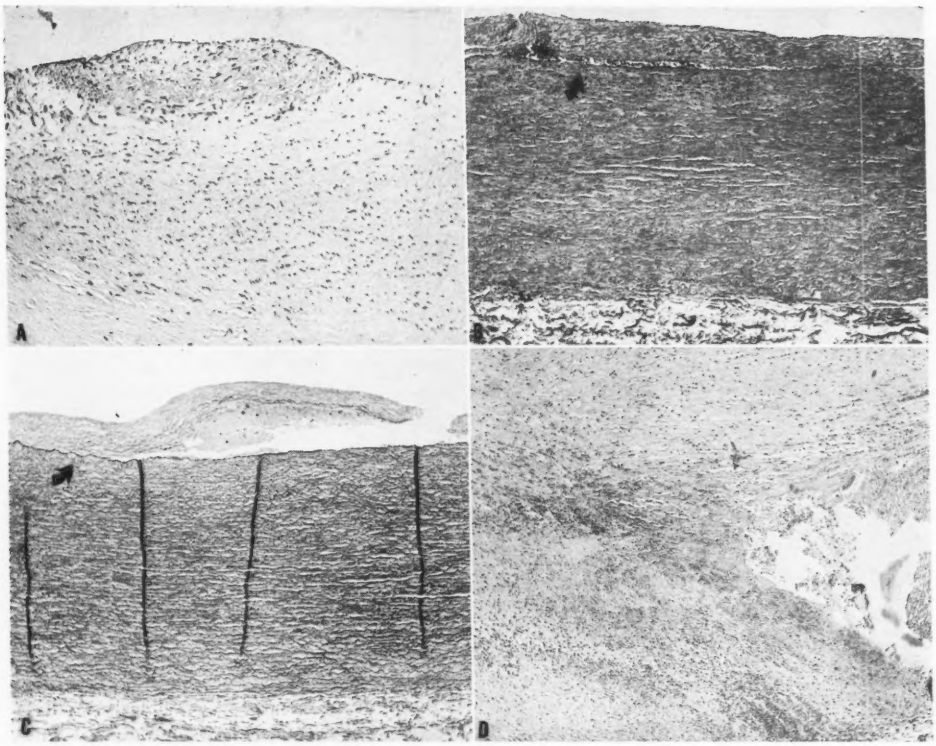


FIG. 2. (AFIP Acc. 639151). (*A*) Stained section showing a small area of intimal hemorrhage with an intact endothelial surface. There are extravasated red blood cells in the subintimal tissue. The hemorrhage is limited to the intima of the aorta. ×70. (*B*). (AFIP Acc. 652262). Laceration of the aorta at the junction of the intima and media along the internal elastic membrane. In this region the integrity of the intimal surface is still preserved. There is a small amount of hemorrhage in the lacerated area. ×50. (*C*) (Same case as fig. 2*B*). Elastic stained section from another region of the aorta showing an aortic laceration with tearing and partial dissection of the intima from the media. The internal elastic membrane is visualized in this section. Note the small amount of intimal hemorrhage and the tear through the media. × 50 (*D*) (AFIP Acc. 639151). A section from the aorta showing a medial laceration with tearing and separation of the elastic lamella and hemorrhage into the adjacent media. Disruption of the media is evident. × 35.

smooth. In a few instances dissecting aneurysm resulted from intimal and medial lacerations with subsequent rupture through the adventitia after dissections of the arterial wall for varying distances. Surprisingly, very few (21) lacerations of the aorta were found in which the trauma involved only 1 or 2 layers of the aortic wall. In these instances they were usually small horizontal or longitudinal tears involving the intima and occasionally extending into the media. Thus in our series the extent of involvement of the aortic wall varied from a simple subintimal hemorrhage to complete laceration of the aorta. The lesions may be classified as follows: (1) intimal hemorrhage; (2) intimal hemorrhage with laceration; (3) medial laceration; (4) complete laceration of the aorta; (5) false aneurysm formation; (6) periaortic hemorrhage.

An evaluation of the gross and histopathologic features of trauma to the aorta requires

an appreciation not only of the normal microscopic structure of the aorta, but also of the possible pathologic alterations that might have preceded the wound. It would be fallacious to assume that all aortas were free from pathologic change at the time of injury. Indeed, our experience with a large series of autopsies in a similar age group in which trauma was not the cause of death indicates that pathologic changes in the aorta, particularly atherosclerosis, are common.

Atherosclerosis was found in our series, but in only 1 instance was it considered to have added significantly to the traumatic lesion. However, medial cystic necrosis of minimal to moderate degree in 3 instances probably made the aorta more vulnerable to unusual stress. Syphilitic involvement of the aorta was noted twice but was not considered a factor in production of the rupture. In neither of these cases was there aneurysmal dilatation of the aorta. Congenital cardiovascular defects were not demonstrated in our series.

Lesions of the Intima

The lesions involving the intimal layer in our series may be grouped as (1) intimal hemorrhage and (2) intimal hemorrhage associated with laceration.

Intimal Hemorrhage

Areas of intimal hemorrhage were described occasionally in association with fatal lesions. They varied in size and often were noted only on microscopic examination (fig. 2*A*). It is probable that lesions of this type occur frequently but are not recognized.

Intimal Laceration with Hemorrhage

This lesion differs in that the endothelial surface of the aorta is broken and the collagenous and elastic fibers of the "subendothelial layer" of the intima are more severely disrupted and separated by hemorrhage (figs. 2*B* and 2*C*). The limiting effect of the internal elastic lamina on the extent of the laceration of the wall is illustrated in both figures. It is lesions of this type that could serve as the nidus of thrombus formation, either bland or septic, with possible peripheral embolization. The break in the endothelial lining might also lead to further dissection.

Lesions of the Media

The tunica media forms the bulk of the aortic wall. The elastic fibers of the media with their great tensile strength and their concentric lamellar arrangement provide much of the resiliency of the arterial wall. The smooth muscle fibers provide the contractile properties and serve to maintain the "vascular tone," but probably contribute relatively little to the over-all strength of the arterial wall. The elastic lamina may be frayed, split, or even destroyed in various diseases, such as advanced atherosclerosis or syphilitic aortitis, and such changes may render it more susceptible to traumatic laceration. The importance of the amorphous intercellular substance of the intima and media has recently been recognized. It is increased in amount in atherosclerosis, and accumulations of this material, often with focal pooling and vacuolization, characterize the lesions of idiopathic cystic medial necrosis of the aorta. Thus, it would appear that an abnormal accumulation of the amorphous intercellular substance must be considered in the evaluation of the effect of trauma on the aorta.

Traumatic Medial Lacerations

Lacerations extending into, but not through, the tunica media (fig. 2*D*) were observed occasionally in this series. Such lesions were described at autopsy, usually in association with other aortic lesions, but sometimes alone. The possibility that a medial laceration might lead to further dissection, rupture, or formation of an aneurysm should not be overlooked.

Lesions of the Adventitia

The tunica adventitia provides a portion of the tensile strength necessary for the maintenance of the normal caliber of the aorta, and through the medium of the vasa vasorum contributes to the sustenance of the arterial wall. It is vulnerable to systemic and local disease.

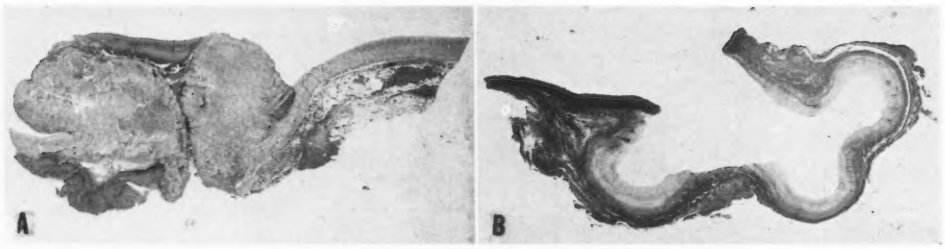


FIG. 3. (AFIP Acc. 147826). (*A*) A recent thrombus superimposed on the site of post-traumatic laceration of the aorta. Note the small fragment of aorta on the surface of the thrombus. The laceration extends through the aorta. X 2½. (*B*) (AFIP Acc. 714264). Elastic stained section showing a healed false aneurysm of the aorta. Note the abrupt termination of the elastic fibers of the aorta at the site of the traumatic laceration. The wall of the aneurysmal sac is composed of fibrous and collagenous connective tissue in which only a rare degenerating elastic fiber is seen. × 2.

Thus, pathologic processes of the adjacent structures, particularly benign or malignant lesions affecting lymph nodes and involving the adventitia secondarily, should be considered in evaluating any traumatic rupture of the aorta.

The traumatic lesions that involved the adventitia of the aorta were of 3 types: (1) traumatic false aneurysm formation; (2) complete aortic laceration; (3) periaortic hemorrhage.

Traumatic Aneurysms

Included under this type are all cases in which aneurysmal bulging of the aortic wall followed complete laceration of the intima and media, and also those in which false aneurysm formed after rupture of all 3 layers. In some instances a distinction between the 2 could not be made with certainty, even on microscopic examination of the wall of the aneurysm.

In cases in which circumferential laceration of the intima and media was complete, a fusiform aneurysmal bulging of the wall of the aorta developed, while in those in which only a portion of the wall was lacerated the bulging appeared as a localized diverticulum or pouch-like formation. The structure varied with the age or duration of the aneurysm. When a repair operation or postmortem examination was performed soon after injury, the pouch of the aneurysm contained a thrombus consisting of fibrin with many enmeshed red blood cells, and usually there was hemorrhage into adjacent tissue. If the patient survived for a few days, the thrombus was soft and fibroblastic proliferation and early vascularization were observed in the wall of the aorta. It is at this stage, when the thrombus is of recent origin, that peripheral embolization is likely. With longer survival, the thrombus may become organized and the wall of the pouch lined with endothelial cells.

Complete Laceration of the Aorta

Complete rupture of the aorta, including the adventitia and the attached connective tissue, was the most common lesion found. Usually death was immediate. However, false aneurysm formation or occlusion of the site of rupture by thrombus (fig. 3) may permit temporary survival.

Periaortic Hemorrhage

Periaortic hemorrhage often accompanied complete rupture or other traumatic lesions of the aorta, but occasionally occurred independently.

AORTIC RUPTURE WITH SURVIVAL

In our series of 275 cases of aortic rupture caused by nonpenetrating trauma the initial survival rate was 13.8 per cent (table 3). Of the 38 patients who survived for various periods, 2 on whom surgical resection of a post-traumatic aneurysm was performed are

TABLE 3.—*Survival times of 275 Individuals with Rupture of the Aorta due to Nonpenetrating Trauma Indicating the Site of Rupture and the Frequency of Immediate Death as Contrasted to the Incidence and Period of Survival*

Sites of rupture	DOA†	Periods of survival														
		>30 min. <1 hr.	1 hr. <6 hrs.	6 hrs. <24 hrs.	1 day <2 days	2 days <4 days	5 days <8 days	8 days <15 days	22 days	50 days	76 days	4 mos.	10 mos.	2–4 yrs.	Cured	Total survived
Ascending aorta	60	1	1	–	1	–	–	–	–	1	–	–	–	–	–	4
Arch	18	–	1	1	–	–	1	–	–	–	–	–	–	–	–	3
Isthmus	101	2	1	3	1	3	3	3	–	–	1	1	1	3	2*	24
Thoracic aorta	31	–	1	–	–	–	1	2	–	–	–	–	–	–	–	4
Abdominal aorta	10	–	1	–	–	–	1	–	1	–	–	–	–	–	–	3
Multiple sites	17	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0
Totals	237‡	3	5	4	2	3	6	5	1	1	1	1	1	3	2	38‡

* Cured by surgery or living.
† Dead on arrival—immediate death or lived <30 minutes.
‡ 273 necropsy cases
2 patients living

still living. As mentioned previously, serious trauma usually produces combined aortic and cardiac injury and other body injury so extensive that death would be inevitable irrespective of the cardiovascular insult. The difference in survival of patients with and without associated cardiac injury is striking. Of the 171 patients with isolated aortic rupture, 34 or 19.8 per cent survived the initial injury, whereas only 4 or 3.8 per cent of the 104 with combined rupture and cardiac injury survived even temporarily. It is of clinical importance that the site of rupture in the first group usually was the isthmus, a region surgically accessible, while in the second group it was more often the ascending aorta that presented a more formidable surgical problem.

The extent of aortic rupture did not appear to have a significant bearing on survival. Nine of the 38 patients who survived the immediate effects of injury had complete transections of the aorta; 8 of the 9 lived longer than 5 days. Only 3 of the 38 died within 1 hour; thus, most lived long enough so that prompt diagnosis and surgical treatment might have offered a good chance of recovery.

Survival is dependent on the formation of a hematoma that is contained by the mediastinal structures and adjacent tissues. The hematoma so formed may continue to dissect the tissues progressively and rapidly, or dissection may be temporarily halted, only to resume hours or days later. In either event, fatal hemorrhage is the final result. A false aneurysm may develop and survival may be prolonged for months or years. In some instances the false aneurysm grows progressively larger over the years, while in a few it remains stable. No matter what the course, the threat of eventual rupture is always present.

CLINICAL ASPECTS

The clinical manifestations of traumatic aortic rupture are by no means uniform. The majority of patients die immediately or within a brief period. However, the 10 to 15 per cent that do survive the initial injury usually present one of several general clinical patterns. Those in critical condition may have obvious and severe body trauma, often orthopedic, or may show little clinical evidence of serious injury. Symptoms suggesting a cardiovascular lesion may not appear until hours or days after injury, often with the development of premonitory signs or symptoms of impending hemorrhage, followed by sudden death. Others, usually those who have survived the period after injury without evi-

dence to suggest aortic injury, may exhibit the signs and symptoms of aortic aneurysm with impending rupture weeks or months later; or, in the absence of significant symptoms, aortic aneurysm formation may be revealed by a routine chest roentgenogram. Rarely, aneurysm with dissection may follow traumatic aortic injury of this type.[5, 17] An unusual complication is subacute bacterial endaortitis, which has been reported by Stryker.[13]

Failure to diagnose the aortic rupture while the patient is still alive is the chief obstacle to proper treatment. In 12 of the 38 cases in this series, the correct diagnosis was considered before death, in 9 because an aortic aneurysm was demonstrable by roentgenogram. This diagnosis is seldom considered in the early postinjury period because of the mistaken concept that a patient could rarely, if ever, survive such a lesion. The realization that this concept is false will remove the major impediment to diagnosis.

Unfortunately, there are no clear-cut early diagnostic features of aortic rupture. The patient's vascular injury is usually overlooked and the more obvious injuries are problems for the orthopedic or neurologic surgeon. Eighteen, or 47 per cent of the 38 patients, had a history of unconsciousness for varying periods of time. Twenty-seven had fractures other than of the ribs, usually of an extremity, and many died from unsuspected aortic rupture during or soon after orthopedic treatment. Fractures of the dorsolumbar vertebrae were found in 34 of the entire series of patients, and in 29 the rupture was definitely related to the site of fracture. Possible aortic rupture should be considered in every patient incurring a dorsolumbar vertebral fracture in a serious accident.

External evidence of chest injury was helpful in arousing suspicion of possible cardiovascular damage, but was often absent even when cardiovascular damage was extensive (fig. 1*B*). In a review of all cases of aortic rupture from this standpoint it was found that 101, or 36 per cent of the 275, had minimal or no external evidence of chest injury, despite the high incidence of rib fracture.

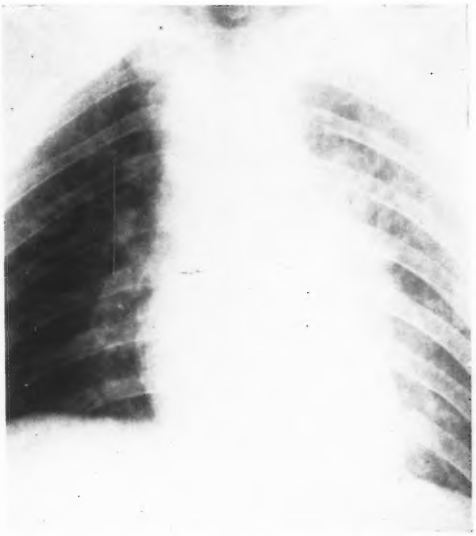


FIG. 4. (AFIP Acc. 709699). (Case 3). Posteroanterior chest roentgenogram demonstrating widening of the mediastinum in a patient who had incurred an almost complete transection of the ascending aorta.

Although many patients were in shock initially, blood pressure was within normal range in 10 and became normal in an additional 19 soon after measures to combat shock were instituted. Rarely were there any specific symptoms or signs of cardiovascular injury. Chest or abdominal pain, dyspnea, tachycardia, hemoptysis, and cyanosis were the more common clinical manifestations. These signs and symptoms were most often attributed to other injuries, frequently to associated pulmonary lesions.

Unexplained hemorrhage and hemothorax with roentgenographic evidence of widening of the mediastinum are the early manifestations of diagnostic importance. The early roentgen signs of rupture of the aorta have recently been described.[19] The most important is widening of the mediastinum (fig. 4). Usually there is associated hemothorax that may be present early or may be delayed. Fractures of the thoracic cage are common, despite a lack of external evidence of injury. Clinical and laboratory evidence of unexplained

hemorrhage has in several instances led to exploratory laparotomy on the assumption that continuing blood loss was due to hepatic or splenic laceration. The possibility of aortic rupture must always be considered in such circumstances.

After the first 24 hours have passed and the patient's condition becomes stable, the probabilities for diagnosis are greatly improved. The signs and symptoms of aortic rupture then resolve into those produced by a mediastinal mass, the hematoma or false aneurysm, and the tendency of this aneurysm to leak blood. This often produces a delayed or recurrent hemothorax, which is the one most important diagnostic feature. Failure to recognize its importance is disastrous, since fatal rupture soon follows. Frequently associated with this finding, although it may occur independently, is the recurrence or aggravation of chest pain caused by further dissection of mediastinal structures and pleura by the enlarging hematoma. The appearance of dysphagia, evidence of tracheal or bronchial obstruction, vena caval obstruction, or the development of hoarseness have been encountered in patients of this series. Impending rupture of the aneurysm into a bronchus may be heralded by hemoptysis with or without associated hemothorax. Roentgenographic examination of the chest at this time may demonstrate that a previously nonspecific widening of the mediastinum now appears as a mass. In one patient of this series, enlargement of the aneurysm was delayed sufficiently long after the accident to suggest a rapidly growing lymphoma or abscess. In other instances, the false aneurysm may remain relatively stable for a prolonged period before evidence of secondary rupture appears. In some cases rupture occurs without prior warning and is catastrophic in extent.

Diagnosis of aortic rupture is easiest in those instances in which a false aneurysm develops and then remains stable and asymptomatic. Routine x-ray examination of the chest is almost always the means whereby diagnosis is made. This was the circumstance in 9 of the patients of this series. The etiology of the aneurysm is suggested when the past history is evaluated in the light of the roentgen finding.

Three cases of the series emphasize the clinical and pathologic features most commonly encountered.

Case 1. AFIP Acc. 128610: This 20-year-old white man sustained a comminuted fracture of the clavicle and an acromioclavicular separation on the right when the truck in which he was riding overturned. There was no other obvious injury and the orthopedic injuries were repaired. Roentgen examination of the chest 1 month later revealed considerable widening of the upper mediastinum, primarily to the right. Repeated roentgen studies demonstrated progressive increase of this widening. Forty-eight days after the injury, evidence of superior vena caval and respiratory obstruction developed with increasingly severe chest pain. Within 24 hours the signs of superior vena caval obstruction were pronounced and the patient was orthopneic with an audible stridor. Within the next 24 hours asphyxia was imminent. Bronchoscopy revealed marked compression of the lower trachea. An emergency thoracotomy was performed, and the aneurysm of the aortic arch that was found ruptured spontaneously during operation. Death occurred 50 days after injury. At necropsy a defect large enough to admit the index finger was noted in the right posterior aortic wall just proximal to the innominate artery. The margins of the defect were smooth and covered with endothelium and communicated with a "false" aneurysmal sac approximately 7 cm. in diameter lying to the right of the superior mediastinum. The sac was filled with partially organized thrombus and was surrounded by considerable fibrosis and edema. The underlying superior vena cava and lower end of the trachea were compressed by the aneurysm. In the right lateral wall of the aneurysmal sac a large tear communicated with the right pleural cavity, which was filled with blood.

Comment. This patient is typical of those in whom orthopedic injuries dominate the clinical picture and vascular injury is not suggested. As in this patient, progressive widening of the mediastinum may be seen in the roentgenograms days after the injury. The rapid development of obstructive symptoms signals the rupture of the aneurysmal sac.

Case 2. AFIP Acc. 639151: This 23-year-old white man was pinned under a wrecked automobile.

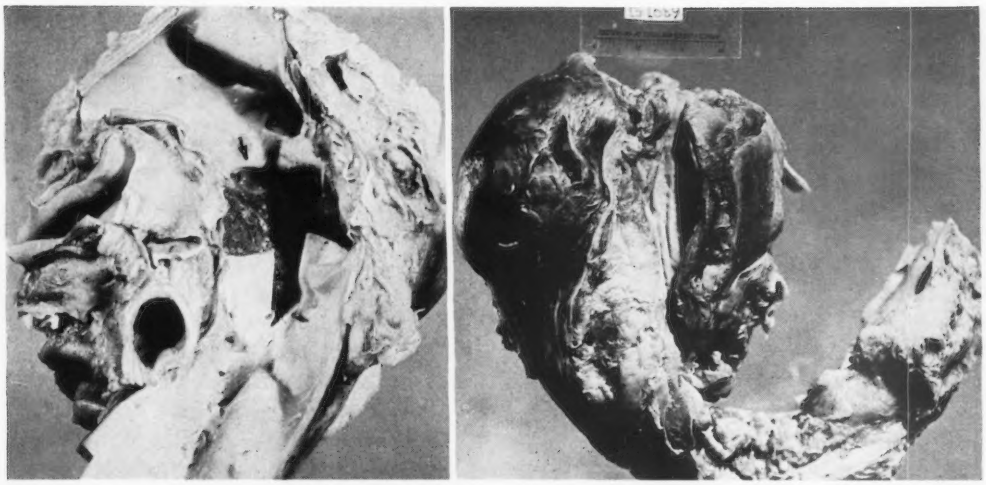


FIG. 5. (AFIP Acc. 639151). (Case 2). *Left, A.* Gross specimen of heart and lungs demonstrating complete transverse horizontal rupture of the aorta 8 mm. below the left subclavian artery in the anterior view (sections for study removed just below site of rupture); and a 6 by 5 by 4 cm. false aneurysm contained by pleura, most clearly seen in the posterior view. *Right, B.* The aneurysm incorporated the recurrent laryngeal nerve. The site of rupture of the aneurysm through a 1.5 cm. rent in the pleura may be seen.

On admission to the hospital, he complained of pain in the right side of the chest and the left thigh. Blood pressure was 105/65, pulse 90 per min., and respiration 20 per min. A few rales were heard in the right lung. There were abrasions of the chest, fractures of the sixth and seventh ribs on the left, and the third, fourth, and fifth on the right, and a compound comminuted fracture of the left femur. The patient was given a whole-blood transfusion and the compound fracture was treated surgically. Postoperatively and until 6 days later the patient did well. Then his temperature rose to 101F., and tachycardia and dyspnea appeared. Because of dulness and absence of breath sounds on the right, thoracentesis was performed with recovery of 500 ml. of blood. The patient became cyanotic, but oxygen therapy brought relief. Hoarseness developed. During the course of the next 24 hours he was given 1,500 ml. of whole blood and by the end of this period the temperature returned to normal and his breathing was normal. Blood pressure was normal and there were no physical signs of hemothorax. However, on the eighth day after injury he suddenly died. Review of chest x-rays taken during hospitalization revealed no definite abnormalities except hemothorax. At necropsy a complete horizontal transverse rupture of the aorta, 8 mm. below the origin of the left subclavian artery, was surrounded by a large hematoma forming a false aneurysm 6 by 5 by 4 cm. that was contained by the pleura (fig. 5). The recurrent laryngeal nerve was incorporated in this hematoma. A rent 1.5 cm. long in the parietal pleura that contained the aneurysm accounted for the massive hemorrhage, which produced left hemothorax of 4,200 ml.

Comment. This is an example of the patient who has no obvious signs or symptoms of aortic rupture when seen initially. The presence of other injury, usually orthopedic, is the obvious and immediate problem. Hours or days later the sudden development of hemothorax is the sign that there is impending rupture of a heretofore silent false aneurysm. Delayed hemothorax appearing suddenly after injury and for no apparent reason should always suggest the presence of a traumatic false aneurysm of the aorta.

Case 3. AFIP Acc. 709699: This 24-year-old white man was the driver of a car involved in a head-on collision. On admission to the hospital, 2 hours later, he was alert and stated that he had not been unconscious. The blood pressure was 55/40 but rose to 150/70 after administration of 1,000 ml. of dextran. Whole-blood transfusion of 500 ml. was then given. Physical examination revealed abrasions of the face, anterior chest, and lacerations of the extremities. Breath sounds were diminished on the right and the

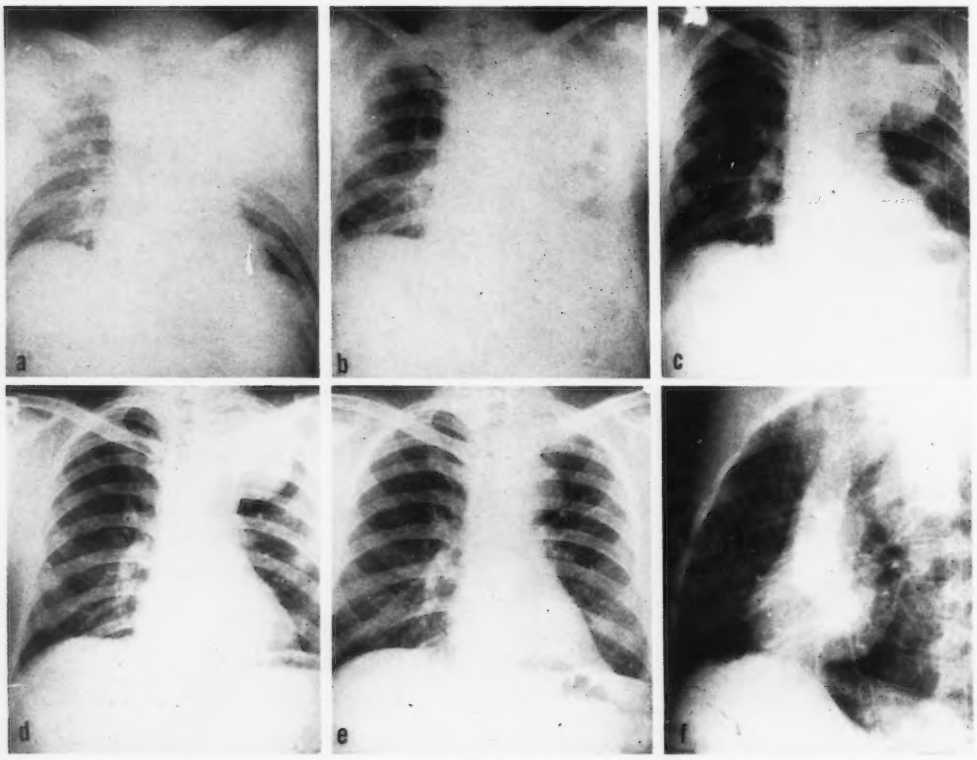


FIG. 6. (WRAH Reg. 3774003). (Case 4). Series of posteroanterior chest roentgenograms demonstrating the development of a false aneurysm of the isthmus region of the aorta following chest trauma: (*A*) immediately after accident; (*B*) 5 days later, a rounded mass becomes evident; (*C*) 17 days after injury, note air injected following thoracentesis demonstrating that area of hemorrhage surrounds developing aneurysm seen as a second rounded density within the upper thoracic shadow; (*D*) 5 weeks after injury; (*E*) 1 year later false aneurysm has formed and surrounding hematoma has resolved; (*F*) venous angiocardiogram demonstrating aneurysm of the aorta, approximately 5 cm. in diameter arising just distal to the left subclavian artery.

patient complained intermittently of anterior chest pain. X-ray revealed a comminuted fracture of the femur, right clavicle, and right fourth rib. The chest x-ray also showed widening of the superior mediastinum (fig. 4). Lacerated wounds of the extremities were sutured. During the next 5 hours the blood pressure remained stable although a sinus tachycardia persisted. The electrocardiogram revealed nonspecific T-wave changes. Following sedation with morphine and Demerol he became comatose with sonorous respiration. His condition remained essentially unchanged until he died suddenly 26 hours after injury. At necropsy the significant findings consisted of extensive hemorrhage within the soft tissues of the anterior and posterior mediastinum with hemorrhage surrounding the arch and thoracic aorta. A transverse irregular rupture, 2 cm. proximal to the origin of the innominate artery, encircled all but 4 mm. of the ascending aorta. Bilateral hemothorax of approximately 1,500 ml. was present. The third, fourth, and fifth ribs on the right anterior were fractured, with laceration of the pleura, and there were fractures of the second and third anterior ribs on the left. The lungs were edematous.

Comment. This case is illustrative of the patient with serious injuries, often of the chest, whose condition deteriorates rapidly or progressively. The only signs of aortic injury may be questionable widening of the medi-

astinum roentgenologically and shock or other evidence of hemorrhage.

Management

Once the diagnosis of rupture of the aorta is made, surgical treatment must be considered. The surgical technics employed have been well established.[33, 40, 41] Review of the available literature reveals 8 reported cases[23, 26–28, 30, 31, 35] of traumatic aortic aneurysm successfully treated by resection. Two additional cases treated by resection and homograft replacement are included in our series. The progression of aortic rupture from a massive hematoma to the formation of a well-defined false aneurysm is well illustrated in these 2 cases.

Case 4. WRAH Reg. No. 3774003: This 27-year-old white soldier incurred a steering wheel injury to the chest and a fracture of the right patella in an automobile accident on December 6, 1953. He was hospitalized immediately and placed in an oxygen tent because of dyspnea. Multiple rib fractures were found on the left side. Transfusions were required because of blood loss due to the development of a left hemothorax, which was considered to be an extrapleural hemorrhage (fig. 6*A-D*). This was treated by thoracentesis. Following operation for the patellar fracture performed on December 17, hoarseness developed but cleared after 3 weeks. The patient was returned to duty but because of repeated symptoms referable to his knee was rehospitalized in November 1954. On direct questioning the patient admitted to slight exertional dyspnea, a mild nonproductive cough, and a pulling sensation in the chest, which he had ignored. A routine chest roentgenogram revealed a left superior mediastinal mass considered to be an aneurysm of the aorta, presumably traumatic (fig. 6*E*). Chest x-rays taken before the automobile accident were reviewed and found normal. Physical examination revealed an increased pulsation of the suprasternal notch and widening of the cardiac base on percussion but no other cardiovascular abnormalities. Blood pressures were 130/90 in the right arm, 134/94 in the left arm, and 144/110 in the left leg. Laboratory studies including the serologic tests for syphilis were normal. The electrocardiogram was normal. A venous angiocardiographic study revealed an aneurysm approximately 5 cm. in diameter involving the aorta just below the subclavian artery (fig. 6*F*). On May 31, 1955, the patient was operated on by one of us (E.J.). The aneurysm arose just distal to the left subclavian artery and was approximately 8 cm. in length and 7 cm. in width. Under endotracheal anesthesia and hypothermia the aneurysm was resected and the defect was repaired with a 6-cm. homologous aortic graft (fig. 7). The patient did well postoperatively and was later discharged from military service in good condition.

Fig. 7. (WRAH Reg. 3774003) (Case 4). False aneurysm as it appeared at time of surgery (*Top, A*); and (*Bottom, B*) aorta following resection and homograft replacement.

Case 5. WRAH Reg. No. 4017011: This 20-year-old white man fell asleep at the wheel of his automobile in October 1955 and the car ran into a tree. He remained unconscious and in shock for 3 hours. Later he complained of headache, pain in the left side of the chest and back, and pain and numbness below the left knee. Epistaxis and vomiting of bloody material occurred. Chest roentgenograms revealed a left

FIG. 8. (WRAH Reg. 4017011) (Case 5). Postero-anterior chest roentgenogram prior to surgery demonstrating the aortic aneurysm of the isthmus region and associated fibrothorax.

pneumothorax and a small right pneumothorax with atelectasis and fractures of the fourth left and sixth right ribs. X-ray evidence of consolidation of the left lower lobe appeared later and the patient continued to run a low-grade fever. It was believed that an organizing fibrothorax (fig. 8) had developed on the left, and on November 9, 1955, a left thoracotomy was performed and decortication was accomplished. An aneurysm of the isthmus region was noted, but at that time surgical correction was not considered feasible. The patient was transferred to Walter Reed Army Hospital. Physical examination there revealed blood pressure of 128/90 in the upper extremities and 130/90 in the lower extremity. Expansion of the left hemithorax was reduced and breath sounds in the lower lung field posteriorly were decreased. At a site just medial to the left scapular border a systolic bruit was heard. A similar bruit was heard anteriorly only with the patient sitting and leaning forward in full expiration. Results of laboratory studies were normal. On January 24, 1956, under general oxygen-ether endotracheal anesthesia with hypothermia, the aneurysm was identified just distal to the left subclavian artery. It was 7 cm. in length and 5 to 6 cm. in width. Resection of the aneurysm was completed and a 7-cm. fresh aortic homograft was used to bridge the resulting defect (fig. 9). The postoperative course was uneventful, and the patient was discharged from the hospital in excellent condition.

Ten other patients in this series were operated upon for various reasons. Some were known to have an aortic aneurysm, others underwent thoracotomy because of unexplained and persistent thoracoabdominal

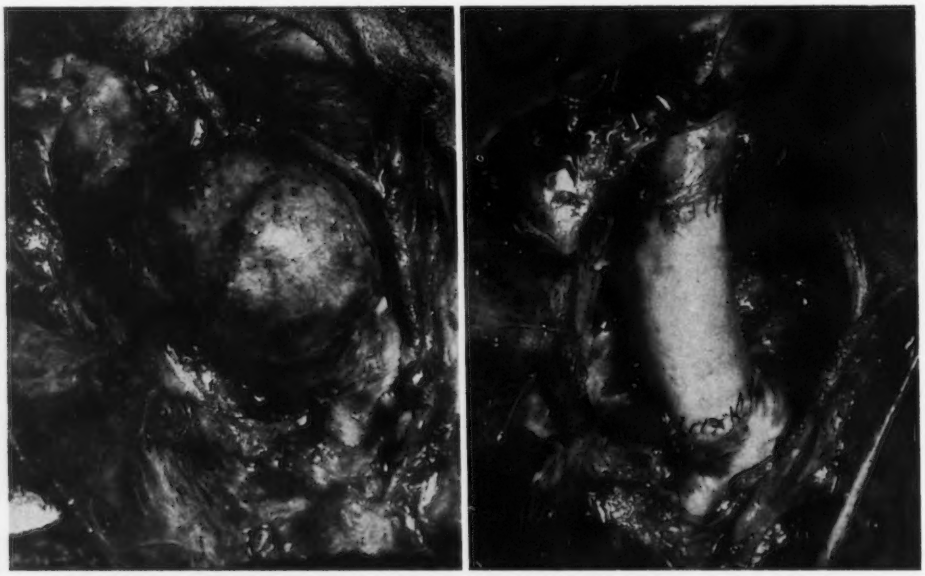


FIG. 9. (WRAH Reg. 4017011). (Case 5). *Left, A.* Photographs obtained at time of thoracotomy demonstrating false aneurysm of the aorta just below the left subclavian artery. *Right, B.* The homograft in place following resection of the aneurysm.

hemorrhage or an enlarging mediastinal mass of unknown nature. In only 3 instances was operation performed soon after the injury. In the other 7 cases treated surgically the patients had survived from 10 weeks to 4 years, and definite aneurysm formation demonstrable by x-ray made the diagnosis certain. In 1 case that has been reported in detail,[23] the postoperative course was complicated by an esophageal pleural fistula and the aortic homograft ruptured at its proximal anastomosis 3 days postoperatively. One patient, whose case is also reported elsewhere,[14] underwent exploratory thoracotomy only to have the aneurysm declared inoperable. Four other patients died during or after thoracotomy from complications of a prolonged surgical procedure. The seventh patient (case 1) underwent late exploratory thoracotomy with rupture of the aneurysm.

If the patient is in extremis when first seen, even a reasonable certainty of diagnosis would rarely justify exploratory thoracotomy. However, in a traumatized patient who is considered to be in relatively good condition and who demonstrates a widened mediastinum on roentgen study, delayed or recurrent hemothorax, or other evidence of unexplained hemorrhage, the diagnosis of aortic rupture and the need for thoracotomy must be seriously considered.

Those individuals in whom a traumatic aortic aneurysm may be demonstrated to be present late in the period after injury and who are otherwise in good condition should, with present day surgical technics, be considered candidates for surgical correction of the aneurysm. However, it has recently been emphasized[36] that the natural course of traumatic aortic aneurysms may be prolonged and before surgical treatment is decided upon its risks must be carefully evaluated.

Summary and Conclusions

A review of 296 cases of nonpenetrating traumatic injury resulting in aortic laceration in 21 and rupture in 275, indicates that this lesion should be suspected more frequently in the traumatized individual.

Study of the causation and the pathology of this aortic injury demonstrates that the commonest site of rupture in this series is at the aortic isthmus, just distal to the left subclavian artery; 45 per cent or 124 occurred at this site.

Almost one fifth of all individuals who sustain traumatic aortic rupture without associated cardiac lesions may be expected to survive at least temporarily. The over-all survival rate in our series was 13.8 per cent (38 of 275 cases) but this figure included those with associated cardiac injury.

A review of the clinical features of the survivors emphasizes that external evidence of trauma may be minimal and initial evidence of definite cardiovascular injury may be lacking. Roentgen signs of a widened mediastinum, evidence of persistent thoracoabdominal hemorrhage, and the appearance of delayed hemothorax are shown to be early diagnostic criteria of aortic rupture.

Prompt diagnosis of traumatic aortic rupture is essential if surgical treatment is to be performed before fatal sequelae develop. Surgical treatment of a traumatic aortic aneurysm that is producing no symptoms and has been demonstrated to have remained unchanged over a period of years should be approached only after careful consideration. Successful surgical resection of a traumatic aortic aneurysm in 2 patients is reported.

Addendum

Since the preparation of this paper 3 additional patients with thoracic aorta aneurysms due to nonpenetrating trauma have been evaluated at Walter Reed Army Hospital. Retrograde aortography was demonstrated to be the most effective roentgenographic means of delineating the extent of these lesions. Two of these patients underwent surgical treatment. In the one the aneurysm could not be resected because it involved the arch of the aorta and its major vessels; the patient died at the time of operation. In the other, whose false aneurysm was a result of almost complete transection of the aorta at the isthmus region, resection with homograft replacement was successful. The operation was performed by means of partial bypass from left atrium to femoral artery with sigmamotor pump.

FIG. 8. (WRAH Reg. 4017011) (Case 5). Postero-anterior chest roentgenogram prior to surgery demonstrating the aortic aneurysm of the isthmus region and associated fibrothorax.

pneumothorax and a small right pneumothorax with atelectasis and fractures of the fourth left and sixth right ribs. X-ray evidence of consolidation of the left lower lobe appeared later and the patient continued to run a low-grade fever. It was believed that an organizing fibrothorax (fig. 8) had developed on the left, and on November 9, 1955, a left thoracotomy was performed and decortication was accomplished. An aneurysm of the isthmus region was noted, but at that time surgical correction was not considered feasible. The patient was transferred to Walter Reed Army Hospital. Physical examination there revealed blood pressure of 128/90 in the upper extremities and 130/90 in the lower extremity. Expansion of the left hemithorax was reduced and breath sounds in the lower lung field posteriorly were decreased. At a site just medial to the left scapular border a systolic bruit was heard. A similar bruit was heard anteriorly only with the patient sitting and leaning forward in full expiration. Results of laboratory studies were normal. On January 24, 1956, under general oxygen-ether endotracheal anesthesia with hypothermia, the aneurysm was identified just distal to the left subclavian artery. It was 7 cm. in length and 5 to 6 cm. in width. Resection of the aneurysm was completed and a 7-cm. fresh aortic homograft was used to bridge the resulting defect (fig. 9). The postoperative course was uneventful, and the patient was discharged from the hospital in excellent condition.

Ten other patients in this series were operated upon for various reasons. Some were known to have an aortic aneurysm, others underwent thoracotomy because of unexplained and persistent thoracoabdominal

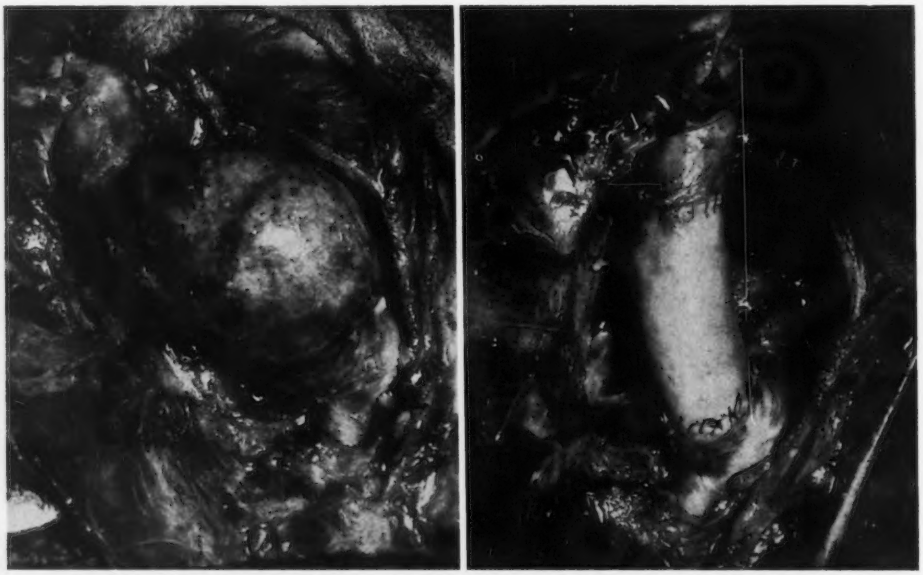


FIG. 9. (WRAH Reg. 4017011). (Case 5). *Left, A.* Photographs obtained at time of thoracotomy demonstrating false aneurysm of the aorta just below the left subclavian artery. *Right, B.* The homograft in place following resection of the aneurysm.

hemorrhage or an enlarging mediastinal mass of unknown nature. In only 3 instances was operation performed soon after the injury. In the other 7 cases treated surgically the patients had survived from 10 weeks to 4 years, and definite aneurysm formation demonstrable by x-ray made the diagnosis certain. In 1 case that has been reported in detail,[23] the postoperative course was complicated by an esophageal pleural fistula and the aortic homograft ruptured at its proximal anastomosis 3 days postoperatively. One patient, whose case is also reported elsewhere,[14] underwent exploratory thoracotomy only to have the aneurysm declared inoperable. Four other patients died during or after thoracotomy from complications of a prolonged surgical procedure. The seventh patient (case 1) underwent late exploratory thoracotomy with rupture of the aneurysm.

If the patient is in extremis when first seen, even a reasonable certainty of diagnosis would rarely justify exploratory thoracotomy. However, in a traumatized patient who is considered to be in relatively good condition and who demonstrates a widened mediastinum on roentgen study, delayed or recurrent hemothorax, or other evidence of unexplained hemorrhage, the diagnosis of aortic rupture and the need for thoracotomy must be seriously considered.

Those individuals in whom a traumatic aortic aneurysm may be demonstrated to be present late in the period after injury and who are otherwise in good condition should, with present day surgical technics, be considered candidates for surgical correction of the aneurysm. However, it has recently been emphasized[36] that the natural course of traumatic aortic aneurysms may be prolonged and before surgical treatment is decided upon its risks must be carefully evaluated.

Summary and Conclusions

A review of 296 cases of nonpenetrating traumatic injury resulting in aortic laceration in 21 and rupture in 275, indicates that this lesion should be suspected more frequently in the traumatized individual.

Study of the causation and the pathology of this aortic injury demonstrates that the commonest site of rupture in this series is at the aortic isthmus, just distal to the left subclavian artery; 45 per cent or 124 occurred at this site.

Almost one fifth of all individuals who sustain traumatic aortic rupture without associated cardiac lesions may be expected to survive at least temporarily. The over-all survival rate in our series was 13.8 per cent (38 of 275 cases) but this figure included those with associated cardiac injury.

A review of the clinical features of the survivors emphasizes that external evidence of trauma may be minimal and initial evidence of definite cardiovascular injury may be lacking. Roentgen signs of a widened mediastinum, evidence of persistent thoracoabdominal hemorrhage, and the appearance of delayed hemothorax are shown to be early diagnostic criteria of aortic rupture.

Prompt diagnosis of traumatic aortic rupture is essential if surgical treatment is to be performed before fatal sequelae develop. Surgical treatment of a traumatic aortic aneurysm that is producing no symptoms and has been demonstrated to have remained unchanged over a period of years should be approached only after careful consideration. Successful surgical resection of a traumatic aortic aneurysm in 2 patients is reported.

Addendum

Since the preparation of this paper 3 additional patients with thoracic aorta aneurysms due to nonpenetrating trauma have been evaluated at Walter Reed Army Hospital. Retrograde aortography was demonstrated to be the most effective roentgenographic means of delineating the extent of these lesions. Two of these patients underwent surgical treatment. In the one the aneurysm could not be resected because it involved the arch of the aorta and its major vessels; the patient died at the time of operation. In the other, whose false aneurysm was a result of almost complete transection of the aorta at the isthmus region, resection with homograft replacement was successful. The operation was performed by means of partial bypass from left atrium to femoral artery with sigmamotor pump.

SUMMARIO IN INTERLINGUA

Un revista de 296 casos de non-penetrante traumatisation que resultava in laceration aortic in 21 e in ruptura aortic in 275 casos indica que iste lesion deberea esser suspicite plus frequentemente in individuos trammatisate.

Le studio del causas e del pathologia de iste typo de vulneration del aorta demonstra que in le serie presente le plus commun sito del ruptura es le isthmo aortic, justo distal al arteria sinistro-subclavian. Isto valeva in 124 o 45 pro cento del casos.

On pote expectar que quasi un quinto de omne individuos que suffre un traumatic ruptura aortic sin associate lesiones cardias va superviver al minus temporarimente. In nostre serie le superviventia total amontava a 13.8 pro cento (i.e. 38 ex 275 casos), sed iste cifra includeva le casos con associate lesiones cardiac.

Un revista del aspectos clinic del superviventes indica que le evidentia externe de trauma pote esser minimal e que al initio omne evidentia de un lesion cardiovascular definite pote esser absente. Es monstrate que signos roentgenographic de allargamento mediastinal, manifestationes de persistente hemorrhagia thoraco-abdominal, e le apparition de un retardate hemothorace es precoce criterios diagnostic de ruptura aortic.

5. Le prompte diagnose de un traumatic ruptura del aorta es essential si on vole que le intervention chirurgic pote esser effectuate ante le disveloppamento de sequellas mortal. Le tractamento chirurgic de un traumatic aneurysmo aortic que produce nulle symptomas e que es demonstratemente inalterate depost plure annos es un interprisa que require le plus circumspecte consideration de omne factores involvite. Es reportate 2 casos de successo in resection chirurgic de traumatic aneurysmos aortic.

REFERENCES

1. SAILER, S.: Dissecting aneurysm of the aorta. Arch. Path. **23**: 704, 1942.
2. KUHN, L. P.: Traumatic rupture of thoracic aorta with review of fifty-five abdominal injuries. Illinois M. J. **47**: 420, 1925.
3. STRASSMANN, G.: Traumatic rupture of the aorta. Am. Heart J. **33**: 508, 1947.
4. SHENNAN, T.: Traumatic (false) aneurysm of the aorta. J. Path. & Bact. **32**: 795, 1929.
5. SAMSON, P. C.: Dissecting aneurysms of the aorta, including traumatic type: Three case reports. Ann. Int. Med. **5**: 117, 1931.
6. WILSON, H., AND ROOME, N. W.: Traumatic shock syndrome following rupture of aorta and multiple fractures. Am. J. Surg. **22**: 333, 1933.
7. HAWKES, S. Z.: Traumatic rupture of heart and intrapericardial structures. Am. J. Surg. **27**: 503, 1935.
8. CORBITT, R. W., AND MATTHEWS, A. R. K.: Rupture of the aorta. West Virginia M. J. **33**: 372, 1937.
9. COLLINS, J. O., AND D'ALESSIO, C. M.: Traumatic rupture of the thoracic aorta. New England J. Med. **219**: 229, 1938.
10. RICEN, E., AND DICKENS, P. F., JR.: Traumatic aneurysm of the abdominal aorta of 27 years duration: Case report. U. S. Nav. M. Bull. **40**: 692, 1942.
11. FORBES, G.: Traumatic rupture of aorta. Brit. M. J. **2**: 400, 1944.
12. TANNENBAUM, I., AND FERGUSON, J. A.: Rapid deceleration and rupture of the aorta. Arch. Path. **45**: 503, 1948.
13. STRYKER, W. A.: Traumatic saccular aneurysm of the thoracic aorta. Am. J. Clin. Path. **18**: 152, 1948.
14. HENNING, B. H., AND AGMAR, A. R.: Traumatic rupture of thoracic aorta: Report of case. Mil. Surgeon **103**: 260, 1948.
15. BRADFORD, B. JR., AND JOHNSTON, F. L.: Traumatic rupture of the aorta: Report of a case in which the patient survived for eighty-one days. Surgery **28**: 893, 1950.
16. RICE, W. G., AND WITTSTRUCK, K. P.: Acute hypertension and delayed traumatic rupture of the aorta. J.A.M.A. **147**: 915, 1951.
17. LEONARD, D. W.: Dissecting aneurysm of the aorta due to trauma. Am. J. Surg. **69**: 344, 1951.
18. HOLLINGSWORTH, R. K., JOHNSON, W. W., AND MCCOOEY, J. F.: Traumatic saccular aneurysm of the thoracic aorta. J. Thoracic Surg. **24**: 325, 1952.
19. WYMAN, A. C.: Roentgenologic diagnosis of traumatic rupture of the thoracic aorta. Arch. Surg. **66**: 656, 1953.
20. KASTL, W. H.: Traumatic rupture of the thoracic aorta. Ann. Surg. **137**: 111, 1953.
21. RODDA, R.: A case surviving six months after traumatic rupture of the aorta. J. Clin. Path. **6**: 145, 1953.
22. JAY, J. B., AND FRENCH, S. W.: Traumatic rupture of the thoracic aorta. Arch. Surg. **68**: 657, 1954.

23. DeBakey, M. E., and Cooley, D. A.: Successful resection of aneurysm of distal aortic arch and replacement by graft. J.A.M.A. **155:** 1398, 1954.
24. Goyette, E. M., Blake, H. A., Forsee, J. H., and Swan, H.: Traumatic aortic aneurysms. Circulation **10:** 824, 1954.
25. Ware, P. F., Adler, R. H., and Lyter, C. S.: Traumatic aneurysm of the thoracic aorta. U. S. Armed Forces M. J. **6:** 1674, 1955.
26. Adams, H. D.: Shunt graft with resection for aneurysm of arch of aorta. J.A.M.A. **159:** 1195, 1955.
27. Stranahan, A., Alley, R. D., Sewell, W. H., and Kausel, H. W.: Aortic arch resection and grafting for aneurysm employing an external shunt. J. Thoracic Surg. **29:** 54, 1955.
28. Julian, O. C., Grove, W. J., Dye, W. S., Sadove, M. S., Javid, H., and Rose, R. F.: Hypotension and hypothermia in surgery of the thoracic aorta. Arch. Surg. **70:** 729, 1955.
29. Zehnder, M. A.: Delayed post-traumatic rupture of the aorta in a young healthy individual after closed injury: Mechanical-etiological considerations. Angiology **7:** 252, 1956.
30. Storey, C. F., Nardi, G. L., and Sewell, W. H.: Traumatic aneurysm of the thoracic aorta: Report of two cases, one successfully treated by resection and graft replacement with aid of a shunt. Ann. Surg. **144:** 69, 1956.
31. DeBakey, M. E.: Personal communication to Storey.[29]
32. Weisel, W., Huttner, W. A., and Becher, I. M.: Unusual aortic arch nonluetic aneurysm; surgical treatment. Wisconsin M. J. **50:** 866, 1951.
33. Bahnson, H. T.: Definitive treatment of saccular aneurysms of the aorta with excision of sac and aortic suture. Surg., Gynec. & Obst. **96:** 383, 1953.
34 Holmes, T. W. Jr., and Netterville, R. E.: Complications of first rib fracture, including one case each of tracheoesophageal fistula and aortic arch aneurysm. J. Thoracic Surg. **32:** 74, 1956.
35. Hardin, C. A.: Resection and orlon graft of multiple aortic aneurysms due to trauma. J. Thoracic Surg. **32:** 251, 1956.
36. Steinberg, I.: Chronic traumatic aneurysm of the thoracic aorta: Report of five cases, with a plea for conservative treatment. New England J. Med. **257:** 913, 1957.
37. Klotz, O., and Simpson, W.: Spontaneous rupture of the aorta. Am. J. M. Sc. **184:** 455, 1932.
38. Oppenheim, F.: Gibt es eine spontane ruptur des gesunden aorta und wie kommt die Zustande. München. med. Wchnschr. **65:** 1234, 1918 cited by Zehnder.[29]
39. Hass, G. M.: Types of internal injuries of personnel involved in aircraft accidents. J. Aviation M. **15:** 77, 1944.
40. DeBakey, M. E., Cooley, D. A., and Creech, O. Jr.: Aneurysms and occlusive diseases of the aorta: Analysis of 203 cases treated by resection and homograft replacement. Henry Ford Hospital International Symposium on Cardiovascular Surgery. Philadelphia, W. B. Saunders Co., 1955, p. 468.
41. Cooley, D. A., DeBakey, M. E., and Creech, O. Jr.: Surgical treatment of aortic aneurysms. Am. Surgeon **22:** 1043, 1956.

Gordon, R. S., Jr.: Unesterified Fatty Acid in Human Blood Plasma. II. The Transport Function of Unesterified Fatty Acid. J. Clin. Invest. **36:** 810 (June), 1957.

A new method has been developed to determine the unesterified fatty acids in blood plasma. This technic has been used in these experiments. During a fast arteriovenous differences were observed. These indicated a net transport of fatty acid from fat tissue to heart, voluntary muscle and viscera. Amino acids given during a fast had a similar smaller effect. The suggestion is made that adipose tissue releases more or less unesterified fatty acids into the blood to preserve "caloric homeostasis." A mechanism that is sensitive to the availability of nonfat calories seems to exist, which controls the release of unesterified fatty acids.

Oppenheimer

The Normal Orthogonal Electrocardiogram and Vectorcardiogram

With a Critique of Some Commonly Used Analytic Criteria

By HUBERT V. PIPBERGER, M.D.

Preliminary standards for the normal orthogonal electrocardiogram and vectorcardiogram were established as a basis for further studies on pathologic series. Schmitt's corrected lead system (SVEC III) was used. The statistical analysis of electrocardiographic and vectorcardiographic data revealed some intrinsic shortcomings of commonly used analytic criteria. As the orthogonal electrocardiogram and vectorcardiogram are interchangeable, inherent advantages and disadvantages of the 2 methods of display could be evaluated in a quantitative fashion.

A PREVIOUS study from this laboratory[1] demonstrated *in man* an enhanced accuracy in the performance of corrected orthogonal electrocardiographic leads as compared to conventional lead systems. In the present investigation, Schmitt's corrected SVEC III leads[2] were applied to 100 normal subjects in order to establish normal standards. Its purpose is to provide at least preliminary data concerning the extent of normal ranges that logically should precede extensive application of the corrected leads to pathologic cases. The results of the present study apply to a great extent also to any other orthogonal lead system with appropriate lead corrections, since it has been shown that the performance of such systems is relatively similar.[1-3]

Scalar and vectorial display was used for the collection of data. Both methods of recording are interchangeable with an orthogonal lead system. Thus, it was possible for the first time to evaluate quantitatively some of the inherent advantages and disadvantages of the display methods. Statistical data were analyzed to evaluate the adequacy of some commonly used electrocardiographic and vectorcardiographic criteria.

TABLE 1.—*Age Distribution of the Subjects Studied*

Age group	Number of subjects	
	Male	Female
15—20	2	4
21—30	31	1
31—40	16	11
41—50	7	14
51—60	5	5
61—69	4	—

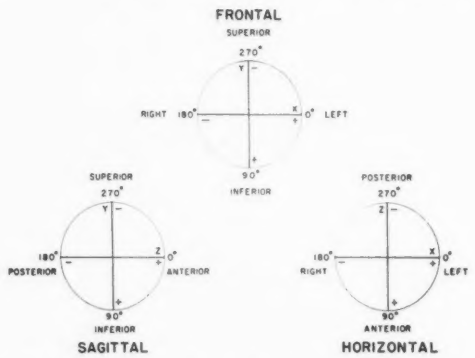


FIG. 1. Reference frame for angular measurements of vector loops in the frontal, right sagittal, and horizontal planes. Plus and minus indicate the polarity of the 3 leads X, Y, and Z as they were used in scalar recordings.

From the Department of Medicine and the Cardiovascular Research Laboratory, Georgetown University Medical Center, Washington, D. C.

Supported by a grant from the American Heart Association.

This work was done during the tenure of a postdoctoral fellowship of the Life Insurance Medical Research Fund.

FIG. 2. Representative vector loops of a normal subject. From left to right: frontal, right sagittal, and horizontal planes. For reference frame see figure 1. Note in the horizontal plane projection the time lag between the instantaneous vectors with largest X and largest Z amplitude. Maximal QRS vectors in the frontal and horizontal planes are not identical.

MATERIAL AND METHODS

The SVEC III lead system[2] was applied to 100 normal subjects, 71 of whom were patients admitted to Georgetown University Hospital for reasons other than heart disease. History, physical examination, chest x-ray, and the 12-lead electrocardiogram did not reveal any evidence for past or present heart disease. The remainder of the subjects were members of the housestaff or medical students without evidence of heart disease. The age and sex distribution of the subjects is shown in table 1.

The scalar leads X, Y, and Z were recorded simultaneously from a cathode-ray oscilloscope with a film speed of 118 mm. per second. Vector loops were photographed in the frontal, right sagittal, and horizontal planes, both by single exposures and on running film. The latter method was used for the identification of time-markings in the vicinity of point E, which are frequently hidden by P and T loops. No measurements were made from these records as the loops become grossly distorted by this method. Due to the previously mentioned difficulties around point E, P loops could not be measured in all subjects.

The electronic characteristics of the recording apparatus have been reported previously.[1] The reference frame used for measurements of loops is given in figure 1. Figure 2 shows a representative record.

Great care was taken to identify accurately instantaneous vectors in loops. A new method was used for this purpose. Time relations are determined more reliably on time-based scalar leads than on any type of loop recordings. Therefore, the incidence in time of the peaks of R_X and R_Y and the nadir of S_Z were measured from the beginning of the QRS complex in simultaneously recorded scalar leads. The corresponding maximal X, Y, and Z vectors of the loops were then marked according to the time measurements from the scalar tracings. As all maximal X, Y, and Z deflections appear twice in vector loops of 3 planes, their incidence in time could be double-checked. When differences were found, a mean value was taken. The error in time could so be reduced to half the interval between time-markings, or 0.00125 second. The described method of identifying instantaneous vectors takes full advantage of the electronic lead integration through vector loops. Vector directions are therefore more accurate than those plotted from scalar deflections.

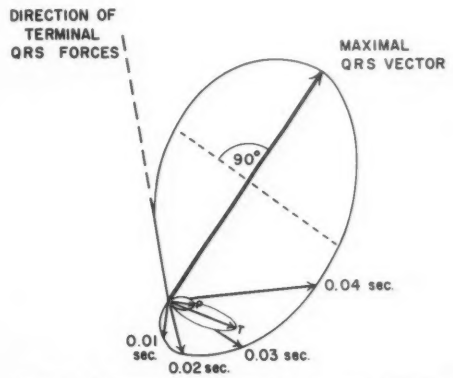


FIG. 3. Schematic diagram of a normal horizontal plane vector loop. The items measured in each loop are indicated. The broken line across the loop represents the loop width. This was taken as the largest distance from one side of the loop to the other, perpendicular to the maximal QRS vector. For the method of determination of terminal QRS forces see text.

The different items measured from vector loops are indicated in figure 3. Maximal QRS, T, and P vectors are those of largest magnitude in each planar projection.

The quantitative analysis of the terminal QRS forces posed several problems. One approach would be the consecutive determination of instantaneous vectors at successive time intervals from

TABLE 2.—*Tabulation of Mean Results and Standard Deviations for the Normal Orthogonal Vectorcardiogram*

	Frontal*	Sagittal	Horizontal
Rotation of QRS-loops (number of cases)	C'ockwise 61 counterclockwise 17 figure 8 or linear 22	C'ockwise 100	Counterclockwise 100
Maximal QRS vectors			
a. direction:	41 ± 14.9°, SE 1.5° (100)	125 ± 36.7°, SE 3.7° (100)	323 ± 40.6°, SE 4.1° (100) (no Gaussian distribution; see figure 2 and text)
b. magnitude:	2.30 ± 0.64 mV, SE 0.06 mV (100)	1.96 ± 0.72 mV, SE 0.07 mV (100)	2.02 ± 0.60 mV, SE 0.06 mV (100)
Maximal width of QRS—loops:	0.58 ± 0.36 mV, SE 0.04 mV (100)	1.30 ± 0.61 mV, SE 0.06 mV (99)	1.56 ± 0.54 mV, SE 0.06 mV (100)
Length to width ratio of QRS—loops:	6.3 ± 6.4, SE 0.6 (100) range 1.1—41.5	1.8 ± 1.0, SE 0.1 (99) range 0.4—6.3	1.5 ± 0.8, SE 0.08 (100) range 0.5—5.9
Direction of terminal QRS forces (for method of determination see text):	193 ± 71.1°, SE 7.2° (97)	191 ± 34.7°, SE 3.5° (100)	256 ± 20.5°, SE 2.1° (100)
0.01 sec. QRS vectors			
a. direction:	scatter too large see table 3 and text	339 ± 28.3°, SE 3.1° (81)	94 ± 26.2°, SE 2.8° (85)
b. magnitude:	0.08 ± 0.07 mV, SE 0.01 mV (71)	0.16 ± 0.11 mV, SE 0.01 mV (69)	0.14 ± 0.11 mV, SE 0.01 mV (74)
0.02 sec. QRS vectors			
a. direction:	scatter too large, see text	1 ± 21.8°, SE 2.2° (97)	84 ± 23.9°, SE 2.4° (96)
b. magnitude:	0.21 ± 0.64 mV, SE 0.07 mV (92)	0.44 ± 0.18 mV, SE 0.02 mV (95)	0.46 ± 0.22 mV, SE 0.02 mV (95)
0.03 sec. QRS vectors			
a. direction:	28 ± 26.7°, SE 2.7° (100)	42 ± 35.6°, SE 3.6° (100)	40 ± 29.8°, SE 3.0° (100)
b. magnitude:	0.80 ± 0.53 mV, SE 0.05 mV (99)	0.75 ± 0.33 mV, SE 0.03 mV (100)	0.90 ± 0.42 mV, SE 0.04 mV (100)
0.04 sec. QRS vectors			
a. direction:	38 ± 12.2°, SE 1.2° (100)	95 ± 34.4°, SE 3.4° (100)	356 ± 26.4°, SE 2.6° (100)
b. magnitude:	1.79 ± 0.65 mV, SE 0.07 mV (100)	1.29 ± 0.56 mV, SE 0.06 mV (100)	1.51 ± 0.57 mV, SE 0.06 mV (100)
Maximal T vectors			
a. direction:	44 ± 12.2°, SE 1.2° (99)	49 ± 20.5°, SE 2.1° (97)	38 ± 21.7°, SE 2.2° (98)
b. magnitude:	0.63 ± 0.22 mV, SE 0.02 mV (98)	0.61 ± 0.25 mV, SE 0.03 mV (97)	0.62 ± 0.26 mV, SE 0.03 mV (98)
QRS-T-angle (measured between maximal QRS and maximal T vectors):	14 ± 9.3°, SE 0.9° (99)	76 ± 42.0°, SE 4.3° (97)	76 ± 45.4°, SE 4.6° (98)
Maximal P vectors			
a. direction:	64 ± 19.8°, SE 2.2° (82)	84 ± 26.7°, SE 3.0° (77)	6 ± 27.7°, SE 3.4° (77)
b. magnitude:	0.28 ± 0.10 mV, SE 0.01 mV (79)	0.26 ± 0.10 mV, SE 0.01 mV (76)	0.20 ± 0.06 mV, SE 0.01 mV (67)

* SE = standard error. For measured items and methods of determination see figure 3. Measurements which appeared unreliable for technical reasons were not included in the tabulation. This occurred frequently in P loops, which were partially or totally hidden by other loops. The number of subjects for each measured item is given in parenthesis. Ranges between lowest and highest values were indicated only when the distribution appeared asymmetric or when the range could not be defined properly by the mean and standard deviations.

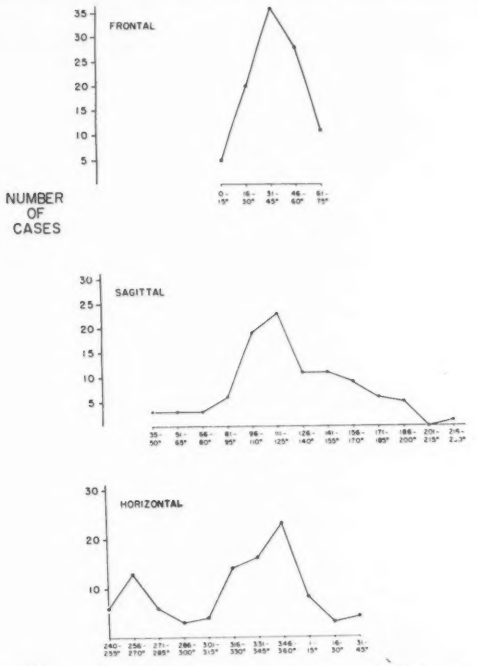


FIG. 4. Distribution curves of maximal QRS vectors in the frontal, right sagittal, and horizontal planes. For the angular reference frame see figure 1. The vectors were grouped in sectors of 15 degrees. The number of cases is given on the ordinate, the sectors on the abscissa. Curves were arranged to show the main peaks on top of each other. Note the small range and symmetric distribution in the frontal plane in contrast to the large scatter and asymmetry of distribution in the other planes. The cases with Rx > Sz are distributed around the larger peak in the horizontal plane. Cases with Sz > Rx form the smaller peak at the left.

the beginning of QRS to the end. Due to differences in QRS duration, the end of the complex would then fall in different time categories. Time measurements backward from the end of QRS lead to similar discrepancies with measurements started from the QRS onset. In this case, the discrepancy is shifted to the midportion of QRS. The attempt to time the terminal QRS forces was therefore abandoned. A tangent to the terminal part of the QRS loop arising from point E was plotted and its direction measured (fig. 3). This method appeared more satisfactory than the arbitrary choice of a point preceding the end of QRS.

RESULTS

A statistical analysis of the QRS, T, and P loops is given in table 2. Most of the listed

TABLE 3.—*Tabulation of Means and Standard Deviations of the Normal Orthogonal Electrocardiogram*

Items measured	Results
I Magnitude of Q_X:	0.11 ± 0.08 mV, SE* 0.01 mV range: 0.015 − 0.36 mV (62)
of Q_Y:	0.14 ± 0.08 mV, SE 0.01 mV range: 0.008 − 0.3€ mV (70)
of R_Z:	0.66 ± 0.31 mV, SE 0.03 mV range: 0.07 − 1.72 mV (100)
II Magnitude of R_X:	1.70 ± 0.49 mV, SE 0.05 mV range: 0.64 − 2.85 mV (100)
of R_Y:	1.55 ± 0.65 mV, SE 0.06 mV range: 0.48 − 3.69 mV (100)
of S_Z:	1.45 ± 0.64 mV, SE 0.06 mV range: 0.38 − 4.50 mV (100)
III Magnitude of S_X:	0.31 ± 0.24 mV, SE 0.03 mV range: 0.03 − 1.17 mV (82)
of S_Y:	0.17 ± 0.18 mV, SE 0.02 mV range: 0.02 − 0.69 mV (76)
IV Q/R ratio in lead X:	0.06 ± 0.04, SE 0.01 range: 0.01 − 0.15 (62)
in lead Y:	0.08 ± 0.04, SE 0.01 range: 0.003 − 0.25 (70)
V R/S ratio in lead X:	10.44 ± 10.25, SE 1.13 range: 1.03 − 47.50 (82)
in lead Y:	14.18 ± 15.54, SE 1.78 range: 0.93 − 64.22 (76)
in lead Z:	0.51 ± 0.27, SE 0.03 range: 0.10 − 1.32 (100)
VI QRS duration (measured from simultaneously recorded scalar leads; see text):	0.093 ± 0.010 sec., SE 0.001 sec. range: 0.074 − 0.113 sec. (100)
VII Time interval between beginning of QRS and beginning of R_X:	0.017 ± 0.008 sec., SE 0.0008 sec. (100)
of R_Y:	0.018 ± 0.009 sec., SE 0.0009 sec. (100)
of S_Z:	0.040 ± 0.008 sec., SE 0.0008 sec. (100)
(all cases)	

TABLE 3—*Continued*

Items measured	Results
VIII Time interval between beginning of QRS and beginning of R_X:	0.021 ± 0.005 sec., SE 0.0006 sec. (67)
R_Y: (only cases where a Q-wave was present)	0.020 ± 0.006 sec., SE 0.0007 sec. (72)
IX Duration of Q_X:	0.018 ± 0.006 sec., SE 0.0008 sec. (67)
of Q_Y:	0.019 ± 0.006 sec., SE 0.0007 sec. (72)
of R_Z: (measured from the beginning of these waves to the beginning of the R or S-waves respectively; not from the beginning of the QRS-complex)	0.038 ± 0.008 sec., SE 0.0008 sec. (100)
X Number of cases without Q-wave in lead X:	33
without Q-wave in lead Y:	28
without R-wave in lead Z:	0
XI Number of cases with	
1. leftward direction of initial forces in lead X:	10
2. isoelectric interval between beginning of QRS and beginning of R-wave but without Q-wave in lead X:	23
duration of this isoelectric interval:	0.013 ± 0.005 sec., SE 0.001 sec. (23)
3. Downward direction of initial forces in lead Y:	13
4. Isoelectric interval between beginning of QRS and beginning of R-wave but without Q-wave in lead Y:	15
Duration of this isoelectric interval:	0.014 ± 0.006 sec., SE 0.001 sec. (15)
5. isoelectric interval between beginning of QRS and beginning of R-wave in lead Z:	23
Duration of this isoelectric interval:	0.007 ± 0.003 sec., SE 0.001 sec. (23)
XII Time interval between beginning of QRS and peak of R_X:	0.044 ± 0.006 sec., SE 0.0006 sec. (100)
R_Y:	0.045 ± 0.006 sec., SE 0.0006 sec. (100)
S_Z:	0.057 ± 0.007 sec., SE 0.0007 sec. (100)
XIII Duration of S_X:	0.026 ± 0.009 sec., SE 0.001 sec. (82)
S_Y:	0.023 ± 0.011 sec., SE 0.001 sec. (76)

* SE = standard error. For polarity of the scalar leads and methods of measurements see figure 1 and text. Results which appeared unreliable for technical reasons are not included in the tabulation. The number of subjects is therefore given for each item in parenthesis. Ranges between highest and lowest values were indicated only when the range was not properly defined by the mean and standard deviation.

data are self-explanatory. The range for the direction of maximal QRS vectors in the frontal plane was relatively small. The distribution of results followed a symmetric Gaussian curve. In the sagittal and horizontal planes, no normal distribution was found (fig. 4). In the latter plane the maximal QRS vectors were distributed around 2 different peaks. This was found to be due

TABLE 4.—*Grouping of 0.01-sec. QRS Vectors of the Frontal Plane According to the Direction of Their Maximal QRS Vectors in This Plane*

Group no.	Sectors of 15° in the frontal plane for grouping of maximal QRS vectors	Mean direction of 0.01-sec. QRS vectors in the frontal plane grouped according to the direction of their maximal QRS vectors
1	0—15°	151 ± 30°, SE 13.4° (5)
2	16—30°	190 ± 87°, SE 21.2° (17)
3	31—45°	243 ± 69°, SE 13° (28)
4	46—60°	258 ± 44°, SE 9.4° (22)
5	61—75°	278 ± 23°, SE 7.8° (9)

Significant differences between the groups (t test):
Group 1 and 3, 1 and 4, 2 and 4: $p < 0.01$
Group 1 and 5, 2 and 5: $p < 0.001$
Group 2 and 3, 3 and 5: $p < 0.05$

These initial vectors were scattered around the whole angular reference frame. Means and standard deviations could be obtained only after grouping. Note the relatively fixed relationship between the direction of 0.01 sec. and maximal QRS vectors. In spite of grouping ranges for the initial vectors exceed those of the maximal vectors.

to a time interval between the peak of R_X and the nadir of S_Z. In the majority of cases, the magnitude of R_X exceeded that of S_Z. In these instances the maximal QRS vector was identical or close to the maximal X vector. In the remainder of the cases the maximal QRS vector coincided closely with the maximal Z vector. A mean time interval of 0.012 second separated the peak of R_X and the nadir of S_Z (table 3, XII). This led to an angular discrepancy of the 2 peaks for maximal QRS vectors of 90° (fig. 4).

The direction of the 0.01- and 0.02-second QRS vectors in the frontal plane varied extremely with a range covering the entire angular scale. A mean direction could therefore not be determined. When the 0.01-second QRS vectors of the frontal plane were separated according to the direction of their maximal QRS vectors, a better grouping was obtained. Most of the subgroups differed significantly (table 4). It was obvious that maximal and 0.01-second QRS vectors were related to each other through their direction. Grouping of 0.02-second QRS vectors in the frontal plane in the same fashion did not lead to significant differences of the subgroups. Ranges of direction for the 0.03 and 0.04-second QRS vectors were considerably smaller, especially the latter.

Directions of maximal, 0.01-second and terminal QRS vectors were correlated with age, relative body weight,[4] and height of the subjects. No correlation was found for any of these comparisons. In the age group beyond 50 years (14 subjects) all maximal QRS vectors of the frontal plane showed an angle of less than 50° with the X axis. Below this age limit a large scatter of QRS directions was found.

A uniform rotation of the QRS loops was found for all cases in the horizontal and sagittal planes. In the frontal plane the rotation was clockwise in 61 per cent, counterclockwise or figure 8 in the remainder of the cases (table 2). No correlation was found between the QRS rotation in the frontal plane and age or relative body weight. A relation, however, existed between rotation of QRS and the direction of maximal QRS vectors. The cases with clockwise rotation showed a mean direction of the maximal QRS vectors of 45 ± 13° and those with counterclockwise rotation of 27 ± 15°. The angular difference between the 2 groups proved significant ($p < 0.001$).

The pertinent data for the orthogonal electrocardiogram are given in table 3. The magnitude of all measured items was higher than for conventional bipolar or unipolar leads. The QRS duration determined from simultaneously recorded leads was 0.093 ± 0.010 second. In many cases, an initial QRS deflection was found only in 1 or 2 leads, whereas other leads showed an initial isoelectric interval. The duration of Q waves in lead X and Y, and of R waves in lead Z, differed therefore as to whether they were measured from the beginning of the QRS complex to the end of the wave, or from the beginning of the wave proper to its end. Both types of measurements have been made (table 3, VII, VIII, IX) in order to demonstrate the discrepancies in results of the 2 methods.

DISCUSSION

The most cumbersome feature of the conventional electrocardiogram and vectorcardiogram is the large normal range for almost all analytic criteria commonly used. A wide

overlap between normal and pathologic obviously is undesirable. Part of the variability of the normal electrocardiogram has been attributed to the inconstancy in direction and strength of conventional effective lead axes.[3, 5] The SVEC III lead system used in this study has been shown in torso models[2, 3] and in man[1] to have relatively constant lead characteristics regardless of positional dipole variations and differences in body build. If a reduction of normal ranges is found with such a corrected lead system, it can be concluded that the large variability of the conventional normal electrocardiogram is indeed due to variations in direction and strength of their effective lead axes. On the other hand, large normal ranges from the use of corrected lead systems would indicate a great intrinsic variability. The extension of normal ranges for corrected lead systems has therefore to be compared with that of conventional lead systems.

1. Configuration of Vector Loops. The configuration of vector loops is difficult to quantitate and remains a descriptive criterion. In the present study, a striking uniformity in configuration of the tracings was found (fig. 2). It was not possible to separate different types of QRS loop configurations, as have been described by Burch and associates[6] for the tetrahedron lead system. Abildskov and Pence[7] reported a similar uniformity in their tracings of a younger age group. From the present study of a relatively small number of subjects in the older age groups it appears that this uniformity is maintained to a considerable extent throughout life. No significant correlations between age and directions of maximal and initial QRS vectors were found. This negative finding, however, needs to be corroborated by larger series.

2. Directions of Maximal QRS and T Vectors in the Frontal Plane. The normal range for the maximal QRS and T vectors in the frontal plane was relatively small. Ranges for QRS up to 140° were found when bipolar and unipolar extremity leads were used.[8] The relatively small range of 75° for QRS and 63° for T as found in this study, strongly suggests that the extreme horizontal and vertical QRS axes of conventional electrocardiographic leads are due to the varying characteristics of these leads in direction and strength.

Comparable small ranges for maximal QRS vectors in the frontal plane have been reported for the 2 cube vectorcardiographic lead systems (Duchosal and Grishman).[9] The main disadvantage of these systems is the weak and variable representation of sagittal forces.[1, 2, 10] Frank's corrected lead system[11] whose performance is very close to the SVEC III[1, 3] showed also a relatively small range for maximal QRS vectors in the frontal plane. The range can be approximated from the elevation angle of the "QRS plane"[12] as reported by Seiden.[13]

The narrow range for the main direction of the heart's electromotive forces is surprising, considering the complex muscular structure of this organ. These findings lead to the conclusion that discrepancies between anatomic and electric heart axes must be considerably smaller when corrected instead of conventional electrocardiographic leads are used.

3. Ranges for Other Scalar and Vectorial Electrocardiographic Criteria. The majority of the remaining parameters measured showed ranges that were not significantly smaller or larger than those reported for conventional leads. Considering the uniformity in configuration this finding was surprising. Many of the wide ranges, however, could be explained by shortcomings of conventional analytic criteria which make them unsuitable for quantitative data analysis.

The direction of the initial QRS vectors in the frontal plane (0.01-second vectors) was found to be a function of the direction of their maximal vectors in this plane (table 4). Measurements of direction and magnitude of these initial forces are meaningful only when correlated with the main spatial direction of the QRS loop. This was pointed out for the spatial vectorcardiogram previously by Wolff and associates.[14] Without taking into account the main QRS direction in a more quantitative fashion, the diagnostic significance of initial QRS vectors and Q waves must necessarily be very limited.

The beginning of the QRS complex when

determined from simultaneously recorded scalar leads varied from one lead to another in a great number of cases. The Q-wave duration taken from a single lead, therefore, does not always indicate the interval between onset of QRS and beginning of R waves. Accurate time measurements were possible only from simultaneously recorded scalar leads. The vector loop display was very unreliable for accurate determinations of initial forces.

No symmetric Gaussian distribution was found for maximal QRS vectors in the sagittal and horizontal planes. Their direction is determined mainly by the largest single deflection of the 2 leads used in each plane. Time lags between the incidence of R_X and R_Y on one side and S_Z on the other caused the large scatter of findings. In 90 per cent of the cases maximal QRS vectors were not identical in all 3 planes. The attempt to determine spatial QRS-T angles from maximal QRS vectors was abandoned as by definition an angle has only 2 sides. Spatial angular discrepancies of maximal QRS vectors from different planes of up to 106° illustrate the fallacies of spatial angle determinations. A QRS vector common to all planes is required for true spatial evaluations. The present situation in "spatial" vectorcardiography could be clarified by abandoning the term "mean" QRS for maximal QRS axes[15-17] as a true mean should include all parameters of the complex, namely amplitude *and* time. The spatial mean QRS vector (S $\bar{A}$ QRS) of Ashman[18] appears as the most satisfactory approach to *spatial* vector analysis. When determined graphically, with reasonable accuracy, this method is very time-consuming. Electronic computation of this vector[19] is limited to a few laboratories. The mean of "half-area" vectors from 3 planes has been found to be very close to S $\bar{A}$ QRS.[20-22] As a graphic method, it combines simplicity and accuracy as the resulting vector is common to all planes.

Maximal T vectors were found to be common to all planes almost without exception. This was due to the narrow and peaked configuration of the T loops. The range of maximal T vector directions in the horizontal and sagittal planes was roughly half of that for QRS (table 2). This relatively small range for the T direction also suggests that the large ranges for maximal QRS vector directions in the sagittal and horizontal planes were due mainly to the inadequacy of the criterion itself.

Planar loop recordings appeared superior to scalar tracings for the determinations of vectors of large amplitude. The electronic integration of different leads greatly improves the accuracy of angular measurements. *Planar* vectorcardiography as used in most laboratories at present, however, does not necessarily lead to a spatial evaluation of vectors unless these are carefully identified in all planes.

In view of the uniformity in loop configurations further reductions of normal ranges appear possible. A re-evaluation of commonly used analytic criteria and recording methods seems to be needed in order to decrease many normal ranges. Explorations and tests of new methods of electrocardiographic data analysis and processing are in progress in this and several other laboratories.[23-27]

Summary and Conclusions

Corrected orthogonal electrocardiographic leads (Schmitt's SVEC III system) were applied to 100 normal subjects in order to establish preliminary normal ranges as a basis for future studies on pathologic series. As such a lead system can be used for electrocardiography and vectorcardiography, both methods of display were used for statistical analysis. Conventional electrocardiographic and vectorcardiographic criteria were applied.

Time relations of the vector loop records could be determined accurately only by the additional use of simultaneously recorded scalar leads. Electronic lead integration through vector loops proved superior for determinations of vector directions. Vectorial and multichannel scalar display appeared as complementary methods and the accuracy of recorded data was largely enhanced by the use of both.

The normal range for the direction of maximal QRS vectors in the frontal plane was approximately half of that for conventional electrocardiographic leads. It was concluded, therefore, that extreme horizontal and vertical QRS axes obtained with conventional leads are due to the skewness of their effective lead axes. In spite of a considerable uniformity of loop configurations most normal ranges of other parameters were not significantly smaller than those of conventional lead systems. This was due mainly to intrinsic shortcomings of the applied analytic criteria.

Amplitude and directions of initial QRS vectors and Q waves were found to be a function of the further sequence of the QRS complex. Their significance can be increased by combined analysis of initial and main QRS vectors. Due to time differences in the onset of QRS in different leads, Q-wave measurements should be re-evaluated.

Maximal QRS vectors (often incorrectly designated as "mean" vectors) were identical in all 3 planes in only 10 per cent of the cases. Large angular discrepancies between maximal QRS vectors of different planes indicated that this criterion cannot be used for spatial vector analysis.

The inadequacy of several commonly used electrocardiographic and vectorcardiographic criteria makes a re-evaluation of data analysis desirable. A decrease of the large scatter of normal findings would improve the electrocardiogram as a diagnostic tool. Further range reductions for corrected orthogonal lead systems appear possible by exploration of more adequate analytic criteria.

Acknowledgment

The author gratefully acknowledges the very helpful suggestions and criticisms of Dr. Edward D. Freis. He is very much indebted to Mrs. Hanna A. Pipberger for her technical assistance and the statistical analysis.

Summario in Interlingua

Corrigite orthogone derivationes electrocardiographic (systema SVEC III de Schmitt) esseva applicate a 100 subjectos normal con le objectivo de establir, de maniera preliminari, limites de normalitate como bases pro futur studios in series pathologic. Proque le systema in question pote esser usate in electrocardiographia e in vectocardiographia, ambe methodos de presentation esseva usate in le analyse statistic. Le criterios electrocardiographic e vectocardiographic usate esseva le criterios conventional.

Le relationes temporal in le registrationes de ansas vectorial poteva esser determinate accuratemente solmente per le uso additional de derivationes scalar a registration simultanee. Le integration de derivation electronic per ansas vectorial se provava superior pro le determination del directiones vectorial. Le presentation vectorial e le presentation scalar a canales multiple pareva esser methodos complementari. Le uso de ambes resultava in un augmento del accuratia del datos registrate.

Le area de normalitate pro le direction de vectores QRS maximal esseva circa un medietate de illo obtenite in derivationes electrocardiographic conventional. Ergo il esseva concludite que extreme axes QRS horizontal e vertical obtenite con derivationes conventional es le resultato del obliquitate de lor efficace axes derivational. In despecto de un considerabile uniformitate del configurationes ansal, le areas de normalitate pro le majoritate del altere parametros non esseva significativemente minus diffuse que in le caso del systemas de derivation conventional. Isto esseva causate principalmente per intrinsec debilitates del criterios analytic usate.

Le amplitude e le direction de initial vectores QRS e undas Q esseva recognoscite como functiones del sequentia subsequente in le complexo QRS. Lor signification pote esser augmentate per le analyse combinate de vectores QRS initial e principal. A causa de differentias temporal in le declaration de QRS in differente derivationes, le mesuration del unda Q deberea esser re-evalutate.

Vectores QRS maximal (frequentemente designate incorrectemente como vectores "medie") esseva identic in omne le 3 planos in solmente 10 pro cento del casos. Grande discrepantias angular inter le vectores QRS maximal in differente planos indicava que

iste criterio non pote esser usate in le analyse de vectores spatial.

Le inadequatia de plure criterios electrocardiographic e vectocardiographic in uso commun rende desirabile un re-evaluation del methodos usate in le analyse del datos. Un minus extense area de normalitate pro le varie parametros meliorarea le utilitate del electrocardiogramma como utensile diagnostic. In le caso del systemas de corrigite orthogone derivationes, un reduction de ille areas de normalitate pare possibile per explorar plus adequate criterios analytic.

REFERENCES

1. Pipberger, H. V., and Lilienfield, L. S.: The application of corrected electrocardiographic lead systems in man. Am. J. Med. In press.
2. Schmitt, O. H., and Simonson, E.: The present status of vectorcardiography. Arch. Int. Med. **96**: 574, 1955.
3. —: Lead vectors and transfer impedance. Ann. New York Acad. Sc. **65**: 1092, 1957.
4. Tables of the Life Extension Institute of New York City. Basle Documenta Geigy, 1955.
5. Frank, E.: Spread of current in volume conductors of finite extent. Ann. New York Acad. Sc. **65**: 980, 1957.
6. Burch, G. E., Abildskov, J. A., and Cronvich, J. A.: Studies of the spatial vectorcardiogram in normal man. Circulation **7**: 558, 1953.
7. Abildskov, J. A., and Pence, E. D.: A comparative study of spatial vectorcardiograms obtained with the equilateral tetrahedron and a "corrected" system of electrode placement. Circulation **13**: 263, 1956.
8. Lepeschkin, E.: Modern Electrocardiography. Vol. I. Baltimore, The Williams & Wilkins Company, 1951.
9. Young, E., Wolff, L., and Chatfield, M. S.: The normal vectorcardiogram. Am. Heart J. **51**: 713, 1956.
10. Frank, E.: A direct experimental study of three systems of spatial vectorcardiography. Circulation **10**: 101, 1954.
11. —: An accurate clinically practical system for spatial vectorcardiography. Circulation **13**: 737, 1956.
12. Schellong, F.: Grundzüge einer klinischen Vektordiagraphie des Herzens. Berlin, Springer-Verlag, 1939.
13. Seiden, G. E.: The normal QRS loop observed three dimensionally obtained with the Frank precordial system. Circulation **16**: 582, 1957.
14. Wolff, L., Richman, J. L., and Soffe, A. M.: The effect of heart position and rotation on the cardiac vector: An experimental study. Am. Heart J. **47**: 161, 1954.
15. Grant, R. P., and Estes, E. H., Jr.: Spatial Vector Electrocardiography. Philadelphia, The Blakiston Company, 1951.
16. Simonson, E., and Keys, A.: The spatial QRS and T vector in 178 normal middle-aged men. Body weight, height, relationship of QRS and T and preliminary standards. Circulation **9**: 105, 1954.
17. Helm, R. A., and Fowler, N. O., Jr.: Studies on the QRS-T angle. Am. Heart J. **46**: 229, 1953.
18. Ashman, R., Gardberg, M., and Byer, E.: The normal human ventricular gradient. III. The relation between the anatomic and electric axes. Am. Heart J. **26**: 473, 1943.
19. Johnston, F. D., McFee, R., and Bryant, J. M.: An integrating circuit for measurement of the areas of the waves in the electrocardiogram. Circulation **2**: 5, 1950.
20. Pipberger, H., Luchsinger, P., Kälin, R., and Schaub, F.: Das räumliche Vektorkardiogramm bei der Hypertrophie des rechten Ventrikels and seine Relationen mit den hämodynamischen Grössen des Lungenkreislaufs. Cardiologia **27**: 65, 1955.
21. —, Kälin, R., and Rossier, P. H.: Vektorkardiographische Untersuchungen an Hypertonikern bei massiven Blutdrucksenkungen durch Hexamethonium. Ein Beitrag zur Theorie des Ventrikelgradienten. Cardiologia **27**: 166, 1955.
22. Pipberger, H. V.: Evaluation of quantitative methods for obtaining mean spatial QRS vectors. Circulation **16**: 926, 1957.
23. Milnor, W. R., Talbot, S. A., and Newman, E. V.: A study of the relationship between unipolar leads and spatial vectorcardiograms, using the panoramic vectorcardiograph. Circulation **7**: 545, 1953.
24. Newman, E. V., McGovern, J. F., and Arnold, T. G.: The important recent advances in electrocardiography. Arch. Int. Med. **96**: 591, 1955.
25. Sayers, B. McA., Silberberg, F. G., and Durie, D. F.: The electrocardiographic spatial magnitude curve in man. Am. Heart J. **49**: 323, 1955.
26. Abildskov, J. A., Ingerson, W. E., and Hisey, B. L.: A linear time scale for spatial vectorcardiographic data. Circulation **14**: 556, 1956.
27. Milnor, W. R.: The normal vectorcardiogram and a system for the classification of vectorcardiographic abnormalities. Circulation **16**: 95, 1957.

PANEL DISCUSSION

GUEST EDITOR: HOWARD B. SPRAGUE, M.D.

Prevention and Management of Cardiovascular Emergencies

The Panel was comprised of the following members: HOWARD B. SPRAGUE, *Boston, Mass.*, MODERATOR; JAMES METCALFE, *Boston, Mass.*; BENJAMIN M. GASUL, *Chicago, Ill.*; LOUIS A. SOLOFF, *Philadelphia, Pa.*; MAURICE SOKOLOW, *San Francisco, Calif.*; and STEWART G. WOLF, JR., *Oklahoma City, Okla.*

The Panel Discussion on prevention and management of cardiovascular emergencies was conducted at the Thirtieth Scientific Session of the American Heart Association held at the Sherman Hotel, Chicago, Illinois, on Friday afternoon, October 25, 1957.

MODERATOR SPRAGUE: Those of you who were here this morning are familiar with the forms and faces of our panelists this afternoon. I am moderator or chairman, and Mr. Dewey Barrett recently said that the position of a chairman is that of a minor official at the bull fight who opened and closed the gates to let the bull in and out. Well, at least like the Portuguese bull fighter we will let the bull live rather than kill him at the end.

I have a great many questions here. I tried to be selective at lunch time. We are going to start with a question to Dr. Metcalfe. "Do you consider toxemia or pre-eclampsia as a cardiovascular emergency? What is the current management of the acute hypertensive episodes accompanying these conditions?"

DR. JAMES METCALFE: I do consider pre-eclampsia as a cardiovascular emergency, at least historically. In the series collected before 1950, about 10 per cent of the maternal mortality in pre-eclampsia was due to pulmonary edema, and a great amount of theoretical work was done without much experimental work trying to explain whether or not this was a myocardial toxemia, as was suggested by Dexter and White among others, or whether this could all be explained by the effect of hypertension.

Fortunately from the standpoint of the population and unfortunately from my own experience, pre-eclampsia has disappeared from our population. I have never seen pulmonary edema in a patient of the Boston Lying-In Hospital or its affiliated service. I have seen pulmonary edema in patients sent to the hospital who have had an atrocious sodium intake. I believe that the decline in toxemia of pregnancy is due to a realization of the role of sodium in its production and to prophylaxis by sodium restriction.

Once pulmonary edema occurs in these circumstances, I assume it would be managed as pulmonary edema in general with more attention to diuresis because these people have a demonstrable large water content although not a large blood volume.

As for the acute hypertensive emergency itself, I would gather that, as in other forms of acute hypertension and hypertensive crises, any of the high potency agents will get you over the acute phase; diuresis and eventually delivery will eradicate the disease.

MODERATOR SPRAGUE: Dr. Gasul, at what age do you discontinue streptococcus prophylaxis in children with rheumatic fever? At what age would you not start the streptococcus prophylaxis program when rheumatic disease is first diagnosed in adults? You may

have to ask someone else to answer the second question.

DR. BENJAMIN M. GASUL: In children we do not discontinue prophylaxis at all. We continue to give it to them until we send them to an adult cardiologist. That we used to do at 12 years. Then we extended it to 14. Now we take care of them up to 15 years of age.

MODERATOR SPRAGUE: Do you think you would be unhappy if the adult cardiologist did not keep up with the prophylactic regimen?

DR. GASUL: This is one time when it is good to be a pediatrician. I do not know.

MODERATOR SPRAGUE: I would like to ask the whole panel this question: Do you continue prophylactic therapy for rheumatic patients indefinitely?

DR. MAURICE SOKOLOW: Frankly, I do not personally. I think up to the age of 30, if a patient has had rheumatic fever during the preceding 5 years, say, we would continue prophylactic therapy. If we saw patients after the age of 30, particularly after the age of 35, who had not had acute rheumatic fever for a number of years, we would probably not start prophylaxis because of the potential hazard from the continued use of the drug. We would, however, see to it that the patient was observed closely, had blood cultures, and was watched for respiratory infections, and if he did not develop streptococcic infection, we would not give it. It is a calculated risk. It is now known that if you use prophylaxis you will prevent streptococcic infection. But acute rheumatic fever is so rare after the age of 30, we would probably not use it.

MODERATOR SPRAGUE: Dr. Metcalfe, do the patients at the Lying-In Hospital have prophylactic therapy?

DR. METCALFE: Yes. I am not a pediatrician and I can only take them another 20 years. Childbearing ends at about 45. So I do not have to make the decision, but I would say unqualifiedly I would put the patient on penicillin and tell the patient to keep on it until something better comes along.

There is one point I would make in this connection: people in the childbearing age have children and children are the best targets in the world for streptococci and everything else. I think that any patient who has ever had rheumatic fever should go back to penicillin when her children get into school.

MODERATOR SPRAGUE: Would you take the patient up at age 45?

DR. LOUIS A. SOLOFF: I agree with Dr. Sokolow's statement with one exception. I let the patient go ahead and use penicillin at any age. In other words, the publicity is so great at the moment and we have no evidence that it will not be good. So I think that if the patient wishes to take penicillin by mouth daily, whether he is 40, 50, or 60, he may certainly do so.

MODERATOR SPRAGUE: Do you disagree with this, Dr. Wolf?

DR. WOLF: We are in a quandary about this, not knowing what is the best thing to do. Very often the patient will settle the thing himself by just discontinuing the taking of penicillin, and if he has not had rheumatic infection for a good many years one is likely not to see it. We are inclined to put special emphasis on the literal interpretation of the meaning of the doctor as a teacher and to give the patient careful instructions about having throat cultures made at times when they do have upper respiratory infections, particularly sore throats. I think that is one of the most important things to get across to the individual.

MODERATOR SPRAGUE: Dr. Sokolow, I will ask you some short questions. After treatment with quinidine for acute paroxysmal atrial fibrillation and sinus rhythm is established, should quinidine be continued indefinitely?

DR. SOKOLOW: That, of course, depends on what caused the atrial fibrillation in the first place. If it were an acute episode, possibly related to infection or acute emotional stress, we would not. We would wait to see whether or not the fibrillation was perpetual. If it occurred in a patient with rheumatic heart disease who has a large left atrium and who may be expected to have recurrent attacks,

we would put him on continuous prophylaxis. If the patient, regardless of the cause, had recurrent attacks of acute fibrillation, we would then perhaps first try digitalis for prevention, and if that did not work we would put him on permanent quinidine therapy.

MODERATOR SPRAGUE: Professor Sokolow, for how long would you have a patient on quinidine?

DR. SOKOLOW: Certainly for 5 years; possibly longer.

MODERATOR SPRAGUE: If no quinidine blood levels are available, what total over-all dosage of quinidine orally gives a toxic level?

DR. SOKOLOW: That varies with individuals, but a safe moderate dose that probably should not be exceeded unless one can do frequent electrocardiograms and observe the patient very closely is probably 3 Gm. a day, and for the person who uses quinidine infrequently probably less than that.

MODERATOR SPRAGUE: I have had patients on much longer than 5 years, but then I am a little older than you are. I have had them on 20 years.

May quinidine be used safely in treating arrhythmias due to digitalis?

DR. SOKOLOW: Yes, as a matter of fact, that was the common form of therapy prior to the recent emphasis on the importance of potassium in digitalis toxicity. Moderate doses of quinidine are quite effective in treating arrhythmias due to digitalis toxemia.

MODERATOR SPRAGUE: If a patient gets procaine amide, then you give one of the others to try to stop it?

DR. SOKOLOW: I would say I think the arrhythmia due to digitalis might be considered to be an irritable arrhythmia whereas an arrhythmia due to procaine amide might be considered to be a depressive one. I think if the patient had atrial tachycardia from either procaine amide or quinidine, I would be very hesitant to use the other drug.

MODERATOR SPRAGUE: Dr. Soloff, how long should one delay mitral commissurotomy in a patient who has mitral stenosis, atrial fibrillation and, recent peripheral embolization, granting indication for commissurotomy exists. Should anticoagulants be used during or after commissurotomy? The peripheral emboli were major factors.

DR. SOLOFF: We would proceed with mitral valvotomy while the patient was in the hospital recovering from atrial fibrillation. About anticoagulant therapy, we would proceed with anticoagulant therapy after operation. We have as yet not had the courage to give it during operation as some of our Swedish colleagues have, so that it might be worth trying in this country. As far as I know, no one has as yet, but we would proceed immediately after operation.

MODERATOR SPRAGUE: If you had a patient who had multiple emboli would you put the patient on anticoagulants for some weeks or months prior to mitral valve surgery, with the idea that you might then be past the period when thromboembolism was likely?

DR. SOLOFF: This raises a very important problem that needs a great deal of discussion. It would be my opinion that the patient who has had multiple emboli—I was thinking in terms of this before—very probably has acute carditis, and is not at that particular time a candidate for mitral valvotomy. We would carry the patient through and make absolutely certain that we were not dealing with acute rheumatic carditis before we would proceed with a valvotomy. However, if he had had a simple stroke, a simple cerebral embolus, we would not hesitate to go ahead with a mitral valvotomy during his stay in the hospital.

MODERATOR SPRAGUE: One other question. What are the indications for prophylactic digitalization, that is, prior to surgery?

DR. SOLOFF: This morning I stated that if an old person has short breath and we are uncertain of the cause of the shortness of breath, it is safe to assume that there might be some underlying heart failure and, therefore, I would proceed with complete digitalization. If in any patient who has heart disease and faints, we are uncertain on the basis of clinical grounds whether there may or may

not be some incipient heart failure and whether the stress of surgery may be too great, I would proceed with digitalization.

I think that the objection to digitalis before operation is based mostly on work done many years ago in which it was suggested that the cardiac output was decreased if the patient who had a normal heart was digitalized. But the patient who has had heart disease, whether he has had heart failure or not, if subjected to a stressful situation, such as an operation, is not a normal patient and does not have a normal heart. The possibilities of doing harm by digitalizing the patient I think are so slim that at least we have never been able to recognize harm from it. So I would be more on the active side of digitalizing any patient when there was a possibility that either some heart failure was present or the stress of the operation would be unusually great.

MODERATOR SPRAGUE: Dr. Wolf, is the bradycardia often seen in acute myocardial infarction a vagal reaction to fear?

DR. STEWART G. WOLF, JR: I think it would be awfully difficult to answer that question. I think it is important to realize that this is a way in which bradycardia can be brought about. The cardiovascular structures are capable of responding to a variety of stimuli, among which are stimuli that emanate from the interpretive areas of the brain.

MODERATOR SPRAGUE: Can you explain atrial fibrillation that occurs in sleep, in patients in whom no organic disease exists?

DR. WOLF: Yes, I think it is very important to realize that the connection is in the interpretive areas of the brain that make a significant experience an effective stimulus to put into operation some bodily mechanisms that do not require consciousness to operate. They do not require consciousness of motion and neither do they require an awareness of a conflict situation; therefore periods of sleep are just as good for the production of these bodily changes in responsive circumstances as waking periods. As a matter of fact, they may be somewhat better, and certainly in studies that have been done of patients with peptic ulcers, the hypersecretion of the stomach is often much more vigorous during the night hours than it is during the day.

MODERATOR SPRAGUE: What about dreams?

DR. WOLF: Dreams would be another way of showing how the individual responds to meaningful events when he is not actually aware of what is going on.

MODERATOR SPRAGUE: Dr. Sokolow, in atrial fibrillation do you use any anticoagulant before conversion of the embolism? How long after beginning the anticoagulant do you attempt conversion?

DR. SOKOLOW: If the patient has no history of peripheral embolism, as a rule we do not give anticoagulants prior to therapy. We have not run into very much difficulty with this technic. If the patient has had a recent embolus, we use anticoagulant therapy first, on the assumption that the recent embolus indicates a recent thrombus which may discharge particles of remnants.

MODERATOR SPRAGUE: How often have you had this happen in your experience?

DR. SOKOLOW: It has happened to me quite rarely. I think we have seen certainly not more than perhaps 6 cases of systemic emboli following conversion in approximately 200 conversion attempts. So that in our own experience it is an instance of approximately one half of 1 per cent of systemic emboli.

MODERATOR SPRAGUE: I mean that this business of arrhythmias can be a real emergency. Would you say that you now attempt to convert patients with more serious cardiac disease than you used to? In other words, are you less fearful in converting sick patients than you used to be?

DR. SOKOLOW: I have considerable respect for quinidine and I think that before I would attempt to convert a patient, I would try to get the patient in the best possible condition and to arrive at a judgment that sinus rhythm would be better for him. I would say that we have a better awareness of the patient who is less likely to be converted. Particularly in the individual with rheumatic heart disease, with mitral insufficiency, who has a

large heart, who is in chronic failure, who has had atrial fibrillation for more than a year, we know that the batting average is not more than 40 per cent even though quinidine is given to toxic levels.

On the other hand, if an individual has had coronary heart disease or hypertensive heart disease our success with conversion is sufficiently high, over 80 per cent in patients whose fibrillation is more than a year—better than 90 per cent if the fibrillation is less than 1 year—that we would attempt conversion in most patients. So that we try to distinguish those patients in whom the likelihood of conversion is good and those patients in whom the likelihood of conversion is poor.

MODERATOR SPRAGUE: Following valve surgery do you always try to convert them?

DR. SOKOLOW: I would say practically always, if the surgeon has been able technically to perform a good mitral valvotomy and the patient is still fibrillating, and certainly every patient who had sinus rhythm prior to mitral valvotomy we try to convert.

MODERATOR SPRAGUE: Is procaine amide as effective when given diluted as when it is undiluted?

DR. SOKOLOW: It is probably less effective when diluted but it is safer. We have had patients who failed to convert when the drug was given very slowly, diluted, say, 25 mg. a minute, who succeeded in having the rhythm converted when the injection was sped up. So that one has to weigh the increased toxicity on giving rapid injections against the decrease in likelihood of success if it is given too slowly.

MODERATOR SPRAGUE: Dr. Metcalfe, what is your experience concerning pregnancies following apparently successful treatment of subacute bacterial endocarditis?

DR. METCALFE: Well, it is not extensive but it is successful. It is uniformly successful. Just off the top of my head, as they say, I would guess that perhaps there have been 10 or 15 of these people who have gone through one or more pregnancies. Usually they have an aortic valve disease or mitral insufficiency, and our experience and success with these valve lesions is considerably better than it is with mitral stenosis. So that I would think that the fact of having subacute bacterial endocarditis would not alter my judgment. What would alter my judgment would be the valve lesions and the functional state of the heart's operation as a result of rheumatic heart disease.

MODERATOR SPRAGUE: I am a little surprised at the good success with aortic valve disease following subacute aortic endocarditis. I would like to know about the panels' experience with this. Are you getting into all sorts of trouble with those who had an ulcerative process in the aortic valves that were "cured" and then developed rapid congestive failure?

DR. SOKOLOW: Of course, I have had the same experience that you are referring to; that is, the patient is cured of bacterial endocarditis and then within the succeeding year develops ventricular failure from increasing aortic insufficiency; but that does not always happen.

MODERATOR SPRAGUE: Does any other member of the panel want to comment on that?

Dr. Gasul, what have been your results in surgery for congenital aortic stenosis?

DR. GASUL: Our surgeon began operating on these about 2½ years ago. I believe that so far he has had about 18 patients. I believe that about 12 of them are alive, but that does not mean that they do not have any evidences of aortic stenosis. Until now he has used the closed method in performing the operation. Starting this coming week he is going to use open cardiotomy for aortic stenosis.

I hesitate to advise an operation on a child with an aortic stenosis unless he is practically in heart failure. We have a patient right now whose diastolic pressure in the left ventricle goes up to 50 and he is going to be operated upon, but unless open cardiotomy is done, I hesitate very much to advise an operation on a child with a congenital aortic stenosis. Most of the cases that we have had, following a successful operation, have evidences of aortic regurgitation.

We have not followed them up long enough—as far as I know, nobody else has followed

them up long enough because the operation is not older than 4 or 5 years—to know how dangerous this aortic regurgitation is. We know of patients who developed pulmonary regurgitation following pulmonary valvulotomy. They got along very well, but there the pressure differential is very different from the development of aortic regurgigation after an operation for aortic stenosis.

MODERATOR SPRAGUE: Dr. Soloff, have you any comment on this?

DR. SOLOFF: No, we do not treat children that way.

MODERATOR SPRAGUE: I might say that a real indication of emergency in aortic stenosis in children in our experience has been the appearance of the inversion of the T wave in the lateral precordial leads. I think that the Children's Hospital experience shows that when that occurs as evidence of left ventricular difficulty, these children are likely to die suddenly.

DR. GASUL: May I disagree with you on that? I think we have quite a number of children who have definite electrocardiographic evidences of left ventricular hypertrophy with inverted T waves, who are acting just like any other normal children, who with left heart catheterization do not necessarily show a large gradient between the left ventricle and the aorta, and we do not advise an operation on these patients.

MODERATOR SPRAGUE: This is a question concerning another real emergency, addressed both Dr. Sokolow and Dr. Soloff. How often have you seen bilateral adrenal hemorrhage alone during anticoagulant therapy?

DR. SOLOFF: I have never seen it as a sole cardiologic finding.

DR. SOKOLOW: Nor have I.

MODERATOR SPRAGUE: Dr. Sokolow, in giving oxygen to emphysema patients would it be wise to give carbon dioxide with it?

DR. SOKOLOW: Carbon dioxide does not stimulate the respiratory center in patients with emphysema and carbon dioxide retention because apparently the respiratory center no longer responds to increased pressure of carbon dioxide in the blood, but only responds peripherally as a result of oxygen lack. Therefore, in patients with emphysema and carbon dioxide retention giving carbon dioxide does not increase ventilation.

MODERATOR SPRAGUE: Would you tell us what drugs are contraindicated in ventricular tachycardia and fibrillation?

DR. SOKOLOW: Well, taking the last part first, I do not know which drugs *are* indicated in ventricular fibrillation. There are no drugs that affect it either one way or the other except for perhaps electric shock to produce cardiac standstill and then to use a different type of cardiac shock to get the heart beating again.

In ventricular tachycardia, it has usually been stated that digitalis is contraindicated because it may produce cardiac irritability and result in ventricular fibrillation. Actually the data to support this statement are pretty scanty, and most of us who have had experience in dealing with patients with ventricular tachycardia, that failed to respond to all other measures and have had cardiac failure, have found that actually digitalis reverses it to the sinus rhythm. So I am not certain in my own mind that digitalis is contraindicated in ventricular tachycardia in spite of the statements to the contrary.

MODERATOR SPRAGUE: Does anyone else on the panel want to comment on this?

DR. SOLOFF: I would like to emphasize what Dr. Sokolow has said. I think it is a very important point because, as Dr. Gasul said this morning, it is some times very difficult to tell the difference between a superventricular tachycardia with intraventricular block and ventricular tachycardia, and therefore it is important for us to know that the patient has not received digitalis. Digitalis is not necessarily contraindicated under certain circumstances. I would go along with Dr. Sokolow, and I have used drugs I believe successfully in this situation.

MODERATOR SPRAGUE: Yes, I think that is a very important point.

I am going to ask Dr. Wolf to tell us in more detail about serum lipid changes with stress.

DR. WOLF: This is not strictly relevant, I think, to the question of emergency, and so I will be very brief. Information at the present time on this subject is fragmentary. A paper is going to be on the program early in the week that I am sure will bring the story further along. But at the moment I think the evidence is good enough to say that the mechanisms that regulate the level of lipids in the blood are just other bodily mechanisms that are connected with and capable of responding to impulses reaching them from the interpretive areas of the brain.

In our own experience when elevations of the serum cholesterol have occurred in association with stressful circumstances in the lives of indivduals who have had well documented coronary occlusions, the lipid protein patterns have indicated that the cholesterol increase is in the beta area rather than in the alpha area. These data are still preliminary, however, and I think it would be a mistake to try to draw too many conclusions from them.

MODERATOR SPRAGUE: Dr. Sokolow, do you agree that a hypotensive reaction due to nitroglycerin is a rare event, considering that many patients take and tolerate up to 40 tablets daily? I have one now taking 150 tablets a day.

DR. SOKOLOW: How one defines rare and infrequent I do not know. In the past year I have seen 2 or 3 patients whose pressure fell considerably. The one that I referred to this morning was a patient who would get nauseated and green and his cardiac pain would increase every time he took nitroglycerin; and we observed that his blood pressure fell to a systolic of 70 even in the sitting position after only 1/200 gr. I quoted Russek, who has particularly studied this problem and found that approximately 10 per cent of the patients have adverse reaction. My own experience has been that.

DR. SOLOFF: I think it is important, since we have a drug as good as nitroglycerin, that we should not fear to use it unless we are absolutely certain that it has a bad effect. It is a very rare person who will develop symptoms due to hypotension when he is taking nitroglycerin, but it is very easy to recognize that patient and to be sure that he is not standing but is sitting down at the time. So I personally think that patients who have angina pectoris should be surveyed and told to take it even though there is some evidence that it may lower blood presuure in the standing position.

MODERATOR SPRAGUE: I am going to agree with both of these gentlemen. However, I did write a paper once on nitroglycerin collapse because I was impressed with the rather frightening and true emergency situation of a patient who is really sensitive to nitroglycerin the first time it is tried. I know of a young man just starting in practice in the last year, and about the first patient he had in his office was a person with angina to whom he gave nitroglycerin in the office. The patient collapsed and proceeded to have such a low blood pressure that it undoubtedly promoted a cardiac infarct at that time.

On the other hand, we have treated patients in acute stages of myocardial infarction, one a colleague of ours with heart block, with repeated doses of nitroglycerin with apparent beneficial effect. So that again people differ.

I think I agree with you, Dr. Soloff, that one of our great troubles is in convincing the patient to use enough prevention because of the knowledge that nitroglycerin is related to dynamite and the idea that it is going to lose its effectiveness, and that a patient who takes this powerful medicine is about done for anyway. I really try to sell them on nitroglycerin more than I do to take it away from them.

Dr. Metcalfe, here is a question about embolic complications associated with rheumatic heart disease occurring occasionally in pregnancy. How would you treat these and what management would you use to prevent recurrence?

DR. METCALFE: I gather that this question is specifically concerned with anticoagulation, and fortunately our experience with this as a complication of pregnancy is very small.

However, on a couple of occasions we have used heparin and Dicumarol after embolic episodes during pregnancy.

There is some animal work that gives a very bad picture of the use of Dicumarol because of its effect on the fetus. This was used in rather large doses, and the only reason for not saying the same thing about the anticoagulant qualities of the other drugs is that not enough experimental work has been done on them. This is clearly a toxic drug, and if you give enough of it you will harm the fetus.

In the 2 instances that I referred to, which constitute the sum total of my experience, we brought the patients to the hospital 10 days before their expected day of confinement, reversed the effect of Dicumarol with K_1 oxide and crossed our fingers until 24 hours after delivery when we reinstated it. I am not sure that this is good but it worked.

MODERATOR SPRAGUE: Dr. Wolf, is it possible that many unstable electrocardiograms may be explained on the basis of emotional stress?

DR. WOLF: I think it is important to realize 2 or 3 things here. The first is that there are certain changes in the electrocardiogram that can be brought about under circumstances of emotional stress. There are a good many that are not. The T-wave changes are particularly those that may occur under these circumstances.

Again I would like to emphasize that this simply means that the heart is capable of reacting to impulses emanating from the interpretive areas of the brain, so that the contribution of the significance of the event to one's clinical and laboratory findings must be taken into account.

MODERATOR SPRAGUE: I think that many of you know the experiments that Dr. Graybiel performed during World War II in coming silently up behind a healthy young man and firing off a gun behind his ear, when he was connected with the electrocardiograph. The patients developed intraventricular block, T-wave inversions, and so on, and certainly this must have come from the soul somehow or other.

DR. WOLF: It is attributed to the direct effect of sound.

MODERATOR SPRAGUE: There were no bullets.

Dr. Sokolow, have you noted hypotension or tachycardia with the use of Demerol before and after operation?

DR. SOKOLOW: Yes, I think this does occur, particularly in older people, in 2 situations: in some older people who have had preoperative sedation that might be more than they needed, and in patients with mitral stenosis preoperatively for mitral valvulotomy. In the latter instance, for example, because of diminished cardiac output the peripheral arterial vasoconstriction is compensatory, and when that is removed by a drug such as Demerol, the blood pressure may fall precipitously and be the primary reason these patients may develop ventricular fibrillation, some times after the Demerol and some times slightly later after induction of the Pentothol.

In older people who have had barbiturates and Demerol, the pressure may fall, and on more than one occasion we have seen such patients and had the surgery delayed or even stopped because of the hypotension that resulted. It is for this reason that many anesthesiologists prefer not to give Demerol preoperatively by the usual subcutaneous method, but to give it very slowly in very small amounts intravenously with a very small needle so as to titrate the amount that the patient needs. Furthermore, they prefer not to give hypnotic drugs prior to the use of Demerol unless the patient requires it.

MODERATOR SPRAGUE: Dr. Soloff, will you comment on the antidiuretic effects of sedatives.

DR. SOLOFF: I think that is a very important subject, particularly when we are dealing with men in the upper age group. Demerol, codeine, and morphine very commonly produce symptoms that can mimic or perhaps actually precipitate prostatic obstruction. Whenever we get a patient who apparently has developed prostatism, we always ask whether he has had any one of the other

sedatives, which in a lesser degree can actually suppress the flow of urine.

The prostatic type of manifestation may also occur in my experience after antispasmodic drugs, such as Banthine.

So I think that is a most important problem, and when we are dealing with very intractable heart failure I always go into the problem of this type of sedative as to the possible cause for suppression of urination.

MODERATOR SPRAGUE: I am glad to have you emphasize that because it can certainly create an emergency or an intractable situation, if you do not understand that this therapy is responsible.

There is another question here for you, Dr. Soloff. It has been said that the effective and toxic doses of digitalis may change after surgery. What criteria do you use in sinus rhythm in questionable cases to decide whether the level of digitalization is proper, too low, or too high?

DR. SOLOFF: That is a very difficult question to answer because we, unfortunately, do not have any criteria to judge digitalization in the patient with normal sinus rhythm except for the critical condition of the patient. If the patient's heart beat is inordinately fast for his temperature after operation, one should, of course, be on the alert for complications. Pulmonary embolism, for instance, may increase the heart rate. If we do not find any acute reason for the rise in the heart rate, then I would be inclined to use a short acting digitalis preparation very slowly. If that is done, one must very carefully watch the patient several times a day for possible overdigitalization. There are 2 things one would look for. For instance, in the conscious patient any impairment of appetite, a patient whose appetite is diminished for any nonapparent reason. The second is the appearance of premature beats. Either of these situations would make me feel that my patient has had too much digitalis and that I have increased it above the average maintenance dose that the patient needs. But it is a trial-and-error method and means very careful observation of the patient several times each day.

MODERATOR SPRAGUE: Dr. Gasul, someone thinks that in the treatment of rheumatic fever you stress the use of steroids contrary to the American Heart report, as to the value of salicylates versus steroids. Will you clarify that?

DR. GASUL: I believe that it is generally accepted now-a-days that that experiment was deficient in some ways; that is, not a sufficient amount of steroid was given, no definite distinction was made between acute carditis and chronic carditis, and it was not given for a long enough period of time. Since the termination of that experiment a number of papers have appeared in the literature emphasizing the fact that if one excludes children with chronic rheumatic carditis—I believe that almost all of us will agree that if a child comes in with a chronic carditis, the steroids are not going to change that situation—if you limit yourself to acute carditis, if you start the treatment early enough, if you give sufficient amounts of steroids for a long enough time, particularly in the severely ill patients, I believe the generally accepted opinion now-a-days—and this includes our experience, too—is that the steroids are superior to the salicylates.

MODERATOR SPRAGUE: Do I hear any dissenters among the panel? I do not dissent.

At the first Cornell conference on therapy, published in 1946, you remember that Dr. Harry Gold examined the bags of seven doctors to see what drugs they carried for emergency use. I thought that 10 years later it might be of value to see what these drugs are and I would ask this panel, if they were now packing their saddle bags and getting on their horses to go out and treat the public, without the great advantages of our teaching hospitals, what they would put into them or if they would change these at all.

Thirty drugs were selected by Dr. Gold from 7 bags, and 12 of these were for cardiac emergencies. I will read the names of the drugs and then I will ask the panel what they would add or subtract from this group: Syrup of ipecac, morphine, digitaline nativelle tablets, ouabain, mecholyl, atropine sulfate, quinidine tablets, quinine dihydrochloride for intravenous use, mercuhydrin, epine-

phrine, nitroglycerin, amyl nitrite, and 4 rubber tubes to be used for tourniquets. Ipecac was put in there maybe partly because of a paper that Soma Weiss and I wrote on treatment of paroxysmal tachycardia. It is a nice, safe way of averting some of the dangers of the other therapies. The ipecac, as you know, is returned quantitatively. We have a short time to ask the panel to add any drugs to the bag.

Dr. Sokolow, have you any pet drugs that you would like to add to this list that I read?

DR. SOKOLOW: Well, I would change a few with the same basic principles. I think that I would use one of the rapidly acting glycosides, such as digoxin, in lieu of the digitalis, because it is faster acting, and possibly eliminate ouabain. Instead of using quinine dihydrochloride I would substitute quinine gluconate in its place. Also Mecholyl is used so infrequently I think that it could be eliminated.

DR. METCALFE: I am surprised that the antibiotics are missing as a group. I suppose that if I had to carry one, I would carry penicillin.

DR. SOLOFF: I just don't own a bag, but I would mention that the 3 drugs that are important, as I see them, are morphine, a very fast intravenous digitalis preparation and I would agree with Dr. Sokolow that digoxin is probably as good as any, and also penicillin which Dr. Metcalfe suggested. I think that most of the other cardiac emergencies can be controlled by means of morphine alone.

MODERATOR SPRAGUE: Dr. Wolf, would you add anything to the bag?

DR. WOLF: I think the doctor's placebo personality has to go along in the emergency, but I would agree with the other changes that have been made.

MODERATOR SPRAGUE: Dr. Gasul, would you add anything?

DR. GASUL: Did you mention one of the most important ones—aspirin?

MODERATOR SPRAGUE: No. As a matter of fact, it was in the bag, but I didn't think it was put in as an emergency drug.

DR. GASUL: I would take aspirin and digitalis.

MODERATOR SPRAGUE: Dr. Metcalfe, what is your objection to applying the generally accepted criteria for selection of cases for mitral commissurotomy during the first and second trimester and avoid their slipping into class IV?

DR. METCALFE: You know this is sort of like "Have you stopped beating your wife." This is a matter of judgment and of opinion, but our experience with mitral valvotomy in pregnancy is as follows: We have had 3 deaths in 300 pregnancies in women with rheumatic heart disease, without doing a single mitral valvotomy. We have had 4 deaths in 14 women who were subjected to mitral valvotomy during pregnancy. Now there is no question that the 14 worst ones might have been picked. All I can tell you is that we did not pick any of them. We have never recommended this procedure during pregnancy. Now part of this is probably a Boston obstinacy and part of it is a conviction that a pregnant woman can get through pregnancy with good medical management. Somebody has to take that stand and I am prepared to defend it.

Another discouraging thing is that we have had 4 maternal deaths in the state of Massachusetts of women who have had successful mitral valvotomy according to the fellows who advised them and supervised them afterwards. They died in the next pregnancy. So that I do not regard mitral valvotomy as an answer to mitral stenosis in that or succeeding pregnancies. I guess that is all I want to say.

DR. SOLOFF: I think that that question should be answered in the way that Dr. Metcalfe did but with an addition. First of all the assumption is being made that mitral valvotomy carries a higher risk in pregnancy than it does in a nonpregnant state. At least in our experience that is not true. In other words, it does not make any difference whether the patient is pregnant or not, the morbidity and the mortality experience is about the same. The answer is, as Dr. Metcalfe put it, however, mainly that our patients do not die during pregnancy with mitral stenosis. We have not had the experience that Dr. Metcalfe

has had, but we have had no deaths in our obstetrical ward ever since Dr. Robert Wilson took over as professor of obstetrics about 9 or 10 years ago. So we know no reason for going ahead with mitral valvotomy during pregnancy.

The other important thing is that when you do get a death in pregnancy, if you should have one with rheumatic heart disease, it is important to ask yourself at what stage of pregnancy did it occur and why. Dr. Metcalfe showed this morning that the extra load of pregnancy occurs somewhere around the eighth month. If you are to attribute the death to mitral stenosis itself and not pregnancy, one should expect death at that time, but patients with rheumatic heart disease and mitral stenosis do not die at that time. If there is any death at all that I have been able to find in the recent literature, it is mostly in the immediate postoperative period. In other words, about 12 to 14 hours after the delivery. So I think that there is perhaps, with extremely rare exception, no indication for mitral valvotomy during pregnancy.

DR. METCALFE: I want to make this point. The success of the pregnancy after mitral valvotomy, either during the pregnancy or the year before, does not mean that the mitral valvotomy was indicated or successful.

MODERATOR SPRAGUE: The final question as we end this discussion once again goes to Dr. Wolf. Every time a prominent national or local person dies of a heart attack, many anxious heart patients visit the office. Is it not important that their electrocardiograms are normal even with anxiety?

DR. WOLF: Yes, I think it is important, but I think that we should be alert to the possibility that the changes we might detect at this time might be transitory changes associated with anxiety.

Paterson, J. C., Mills, J., and Moffat, T.: Vascularization of Early Atherosclerotic Plaques. Arch. Path. **64:** 129 (Aug.), 1957.

The authors present the results of studies in man of early aortic atherosclerotic lesions. Structures with the general form of capillaries were demonstrated in the superficial layers of the intima by use of the alkaline phosphatase staining technic for endothelium. In 1 instance, red blood cells were found within a structure that showed enzyme activity. These vascular structures were interpreted as representing an extremely early feature of the disease. The foam-cell accumulations, the fibrous-tissue proliferation, and the deposition of hemosiderin, which are all found in the earliest atherosclerotic lesions, may be explained by recurrent hemorrhages from the rupture of "high pressure" intimal capillaries.

MAXWELL

CLINICAL PROGRESS

Management of Spontaneous Intracranial Subarachnoid Hemorrhage

By H. Thomas Ballantine, Jr., M.D., and David M. Klein, M.D.

UNTIL recently many clinicians considered subarachnoid hemorrhage a diagnostic entity. Since no specific form of treatment was available regardless of the underlying pathology, a painstaking inquiry into etiology appeared to have more academic than practical value. This fact and the high mortality of patients treated only by bed rest and supportive therapy (table 1) often led to a relative lack of interest in the problem.

It is becoming increasingly apparent, however, that a more vigorous therapeutic approach can be beneficial if the specific cause of the bleeding can be discovered. As with all relatively new concepts, differences of opinion concerning details of diagnosis and treatment have produced a massive and predominantly confusing body of literature. From a critical review of the written evidence and our own experiences, we have attempted to fashion a rational approach to this problem for the physician who must currently choose a therapeutic regimen for his patient.

Etiology and Incidence

Bleeding into the intracranial subarachnoid space is a finding common to a variety of pathologic states, both local and systemic. Among the more common local causes are trauma, intracranial aneurysm of the "congenital," "arteriosclerotic," and "mycotic" varieties, angiomatous malformation, "hypertensive" and "spontaneous" intracerebral hemorrhage, and tumor. Systemic diseases that must be considered in the differential diagnosis include sources of septic embolization, such as bacterial endocarditis, and the causes of generalized bleeding tendencies, such as the blood dyscrasias and scurvy.

By use of the term "spontaneous" we are restricting this discussion to those instances of subarachnoid hemorrhage due to an intrinsic fault in the cerebrovascular tree. Thereby we exclude bleeding secondary to trauma, neoplasm, and the systemic diseases. The literature is often confusing in reference to this definition, particularly in regard to the inclusion of hypertensive-arteriosclerotic cerebral hemorrhage with subarachnoid extension. Since the latter entity is common and carries a high natural mortality, its inclusion, whether deliberate or unwitting, will markedly affect any statistical conclusions. Most authors have attempted to eliminate this large group, but in many cases presenting with subarachnoid hemorrhage differential diagnosis is difficult. Individuals with hypertension can bleed from anomalies of the intracranial circulation. Furthermore, intracranial bleeding may of itself raise blood pressure. For these reasons and since specific therapy is occasionally available for this condition, we consider that hypertensive subarachnoid hemorrhage should be included in the group under discussion. For clearer presentation of the other etiologic groups, and for consistency with existing reports, however, we must attempt to separate hypertensive hemorrhage in statistical analysis.

In surveying the literature Walton[1] concluded that nontraumatic subarachnoid hemorrhage accounts for about 8 per cent of

From the Department of Neurosurgery, Massachusetts General Hospital, Boston, Mass.

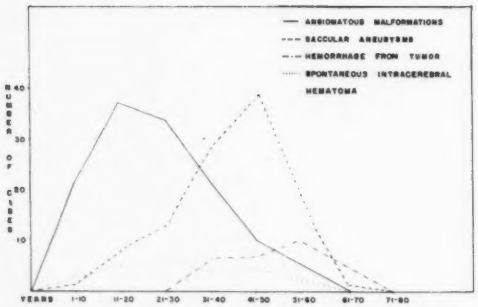


FIG. 1. The distribution of certain intracranial vascular lesions charted as a function of the age of the patients at onset of symptoms (after Tönnis[2]).

cerebrovascular disease seen clinically. If neoplastic and systemic causes are eliminated, 4 basic etiologic groups are found to be responsible for nearly all spontaneous bleeding into the subarachnoid space: hypertensive arteriosclerotic cerebral hemorrhage, "spontaneous" intracerebral hematoma, angiomatous malformation, and intracranial aneurysm.

It is difficult to assess from published reports the number of cases comprising the first group. Excluding this group, it is generally agreed that the other diagnostic categories are responsible in the following order of frequency: "spontaneous" intracerebral hematoma 9 per cent, angiomatous malformation 11 per cent, and intracranial aneurysm 80 per cent. These ratios are only approximate, since autopsy figures are influenced by differing mortality rates for the 3 conditions, and in the living patients angiography does not reveal each type of lesion with equal facility. Furthermore, the age of the patient population will influence the frequency with which each lesion is seen. Hypertensive hemorrhage will predominate in a home for aged couples, arteriovenous malformation in a children's hospital. The importance of considering the patient's age when attempting to arrive at an exact diagnosis has been graphically presented by Tönnis[2] (fig. 1).

DIAGNOSTIC FEATURES

The onset of subarachnoid hemorrhage is sudden, usually with headache, stiff neck, and

TABLE 1.—*Mortality Following Spontaneous Subarachnoid Hemorrhage in Patients Treated by Bed Rest and Supportive Therapy**

Per cent of total	Patients	Source of information
Total mortality during acute illness (8 wk.) 45	1637	References: 1 (summary),36
Total mortality after an average of 5 years..57	919	References: 1, 5-8
Late mortality (recurrent hemorrhage).....12	From above percentages	
Late mortality in survivors of acute illness ..22	From above percentages	
Recurrent bleeding first 8 weeks.....22.5	592	References: 1, 6
Mortality recurrent bleeding first 8 weeks....67	164	References: 1, 6, 8, 36
Gross mortality contributed by early recurrent bleeding.....15	From above percentages	
Gross mortality contributed by original hemorrhage.....30	From above percentages	

* Patients with hypertensive hemorrhage are excluded; the mortality in these patients is over 90 per cent.

altered consciousness, the latter varying from a minimal reduction in awareness to profound coma. Bloody cerebrospinal fluid, usually under increased pressure, is obtained by spinal puncture. In cases of cerebral thrombosis and embolism, however, the clinical picture may be similar: sudden neurologic defects are usual, the patient occasionally complains of headache, and coma can occur. Therefore, the first procedure for an exact diagnosis in a case of "stroke" is a careful lumbar puncture. If a needle of a small caliber is employed, if little or no cerebrospinal fluid is lost, if manometric determinations are carried out *without jugular compression*, and if only 1 to 2 ml. of cerebrospinal fluid are slowly withdrawn, lumbar puncture is safe even if intracranial pressure is increased.

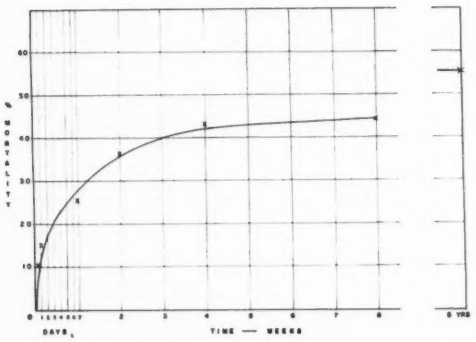


FIG. 2. Cumulative mortality from primary or recurrent subarachnoid hemorrhage charted as a function of time from first bleeding. Data were obtained from Walton's[1] series of 312 patients with subarachnoid hemorrhage from all causes exclusive of hypertensive-arteriosclerotic brain hemorrhage. Survivors were observed for periods varying from 1 to 12 years (average 5 to 6 years) after the original hemorrhage. However, only those deaths which occurred within 5 years of the first hemorrhage are included in this tabulation.

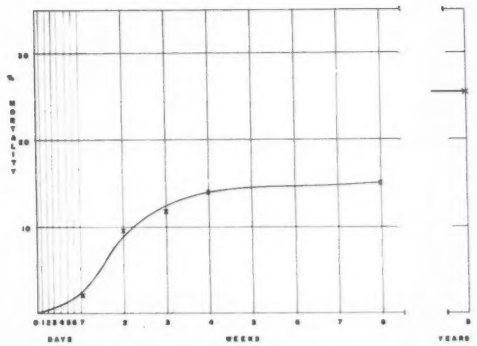


FIG. 3. The cumulative mortality from recurrent subarachnoid bleeding within 5 years of the initial hemorrhage, as reported by Walton[1] for 312 patients with subarachnoid hemorrhage from all causes exclusive of hypertensive-arteriosclerotic brain hemorrhage. Patients in this series were observed for periods varying from 1 to 12 years (average 5 to 6 years) after the original hemorrhage. However, only those deaths due to recurrence of bleeding within 5 years of the first hemorrhage are included in this tabulation. Note the sharp rise in the death rate from the first through the third week after ictus.

COURSE OF SUBARACHNOID HEMORRHAGE TREATED BY BED REST AND SUPPORTIVE THERAPY

More than 9 of 10 individuals with arteriosclerosis and hypertension die within a few hours or days after rupture of a cerebral artery, if hemorrhage has been extensive enough to penetrate into the subarachnoid space.[3, 4] The fate of those patients whose subarachnoid hemorrhage results from the other 3 causes previously listed has been extensively reported by many authors (table 1). The data compiled by Walton[1] are representative and include much other helpful information. Figure 2 has been derived from his reports concerning 312 patients treated by bed rest and appropriate supportive therapy. Approximately 15 per cent of these patients were dead within 24 hours of the ictus, 26 per cent died within 1 week, 45 per cent within 8 weeks.

Figure 3 illustrates the mortality resulting from recurrent hemorrhage and emphasizes the "danger period" 1 to 3 weeks after the initial episode. It is at this time that the physician, gratified at the continuing recovery of his patient, may be shocked by a sudden unexpected fatal outcome.

It has been postulated that reflex vasospasm induced by the first hemorrhage disappears over the early period and that the removal of its protective effect is responsible for secondary hemorrhage. This early recurrence is most frequent in the second and third weeks of convalescence. Several bouts of recurrent bleeding may be seen in the same patient. A second bleeding during the first period of hospitalization (usually 6 to 8 weeks following the original ictus) is responsible for one third of the mortality of this period: 15 per cent of Walton's entire patient population. As to late prognosis, of the 55 per cent surviving the 8 weeks, 19 per cent (10.5 per cent of the entire population) died from "late" recurrent bleeding within 5 years, the majority of these within 1 year. It should be noted that a third of Walton's survivors were not observed for a full 5 years after the original hemorrhage. Had this observation period been fulfilled in every case, there might have been a greater mortality reported. Deaths from recurrent hemorrhage

have been reported after as long as 30 years.[5]

Thus at least 55 per cent of these unfortunate patients are dead after 5 years, 30 per cent with the initial bleeding and 25 per cent from early or late recurrence. Primary concern with such an appalling mortality overshadows any detailed consideration of the survivors' condition, but it should be noted that of 348 patients reported in the literature[1, 5-8] to have survived an average of 5 years, 43 per cent were seriously impaired. These figures for the natural course of the syndrome are in agreement with the conclusion of Ask-Upmark and Ingvar: of those suffering subarachnoid hemorrhage, only 1 patient in 5 will ultimately make a good recovery.[5]

Pathophysiology in Relation to Mortality

Although important differences in prognosis and therapy are found when the major causes for spontaneous subarachnoid hemorrhage are considered separately, they have certain important features in common. All subarachnoid hemorrhage is consequent to rupture of a vascular channel, blood being released either directly into the subarachnoid space or rupturing into it secondarily after parenchymal hemorrhage. Subarachnoid bleeding per se is responsible for no significant part of the mortality. Two factors, alone or in combination, account for the majority of the neurologic defects or deaths that occur: primary destruction of brain tissue by the hydrostatic pressure of the escaping blood, and the secondary effects of an intracranial hematoma, which acts as a space-taking lesion. The physician is usually powerless to alter the first of these phenomena; he can often deal effectively with the second.

Any clinically significant intracranial hematoma will shift the brain from its normal position in the skull and alter its relation to the tentorium, the rigid membrane that separates the posterior and middle fossae. If there is a marked lateral displacement of the brain, the medial portions of the temporal lobes may herniate through the tentorium, causing pressure upon and necrosis of the midbrain. Similarly, a downward shift may cause the cerebellar tonsils to herniate through the foramen magnum, producing pressure necrosis of the medulla. These complications are manifested by rapidly deepening coma, pupillary inequality (if there is unilateral temporal lobe herniation), bilateral Babinski responses, episodes of hyperextension rigidity, and death. Evacuation of the hematoma early, when the effects of midbrain or medullary compression are reversible, is often a life-saving procedure. It should be borne in mind that this is equally true for the treatment of intracerebral hematoma without subarachnoid extension.[9]

Reflex spasm of vessels adjacent to a bleeding point is observed in many parts of the body, and the brain is no exception. In one view, this reflex may be regarded as protective against further hemorrhage. On the other hand, local constriction may be so severe, especially if superimposed upon the already narrowed vasculature of a hypertensive and arteriosclerotic patient, that areas of cerebral ischemia or infarction may be produced. On angiography, vasospasm adjacent to a bleeding point may cause nonfilling in this portion of the vascular tree, thwarting diagnosis. Observations at surgery and by carotid angiography have shown that this spasm diminishes gradually after the bleeding episode and is minimal or absent after the third week.[10]

In addition to the 2 prime causes of immediate mortality, overwhelming brain damage and the effects of intracerebral hematoma, a third factor, recurrent bleeding, may be responsible for most of the late mortality from subarachnoid hemorrhage. This phenomenon is seldom seen with hypertensive hemorrhage, owing to the high initial death rate. It is quite common in cases of aneurysm and angiomatous malformation. At least 50 per cent of the total mortality from ruptured aneurysms is thought to be due to recurrent episodes of hemorrhage. Repeated bouts of bleeding are even more common with angiomatous malformation but they appear to be less lethal.

These differences in susceptibility to and mortality from repeated episodes of hemorrhage exemplify the necessity for separate consideration of each of the major causes of subarachnoid bleeding.

Primary Intracerebral Hemorrhage with Subarachnoid Extension

Intracerebral hematomas rupture into the cerebral ventricles or subarachnoid space in as many as 75 per cent of cases.[3] Two types of intracerebral hemorrhage are now recognized: one that is apparently secondary to hypertension and arteriosclerosis, and a rarer "spontaneous" variety of bleeding in which the cause is not always apparent.

Hypertensive hemorrhage usually occurs deep within the cerebral hemispheres, particularly in the basal ganglia. Arterial degeneration and sustained systemic hypertension are presumed to be the important factors giving rise to this type of bleeding. Why the arteries of the brain are more prone to rupture than the extracranial vessels, and what the exact nature of the arterial degeneration is, are questions as yet unanswered. No form of therapy is currently available to reverse the worsening course of the patient who is rendered immediately or rapidly unconscious by brain hemorrhage and who develops signs of brain stem compression shortly thereafter.

Within this hypertensive-arteriosclerotic group, a less virulent form of the illness is occasionally seen. Here the patient is at first only transiently unconscious or perhaps only slightly obtunded. There is, however, a definite neurologic defect that usually progresses over a period of 2 or 3 days, during which time the state of consciousness gradually deteriorates. Lumbar puncture reveals the cerebrospinal fluid to be under increased pressure, and red blood cells are present in varying concentration. Finally, within 3 to 7 days, death usually ensues as a result of midbrain compression from the intracerebral clot. These hematomas frequently originate in the white matter of the frontal, temporal, or parietal lobes. Evacuation prior to the onset of signs of midbrain compression can be life-saving. It is our opinion that wider recognition of this variety of hypertensive bleeding might have some beneficial influence on a mortality rate that is more than 90 per cent.

Spontaneous Intracerebral Hematoma

This condition is usually seen in younger patients (fig. 1) and the diagnosis implies the absence of a history of significant hypertension. The course is similar to that described above for the more benign form of hypertensive hemorrhage, with gradually progressing neurologic signs, deepening coma, and death in 3 to 7 days from brain stem compression if no treatment is instituted. At postmortem examination the bleeding point is difficult to identify. With careful histologic preparation, however, some of these cases of "spontaneous" hemorrhage can be demonstrated to originate from minute, deeply seated vascular malformations. It is reasonable to believe that in many more cases the small malformation has been obliterated by its own bleeding.[11] Odom et al.[12] reported 14 cases of this syndrome; in 10 patients the hematoma was evacuated and all 10 survived. The 4 patients who were not operated upon died. These hematomas are as uniformly fatal as those produced by hypertension if "conservatively" handled.

Cerebral Angiomatous Malformation

While this entity has certain well-defined clinical and pathologic features, its origin and developmental history are disputed. As a result many descriptive terms have been used for the same basic entity: arterial, arteriovenous, or venous angioma or hemangioma; telangiectasis; arteriovenous hamartoma, aneurysm, or malformation; anastomotic aneurysm or angioma.[13] These lesions are nearly always made up of rather large, tortuous arteries and veins with multiple cross-communications, fed and drained through a lesser number of widely dilated vessels. The lesion may be quite superficial. Frequently, however, it is deeply seated in the cerebrum and wedge-shaped, extending

from a ventricle to the cortex. Hemorrhage from these lesions can be intracerebral with or without subarachnoid extension, or primarily subarachnoid.

Common symptoms prior to bleeding include unilateral recurrent headache, epileptiform seizures (usually focal), and localized weakness. Any combination or sequence may be seen; the first manifestation most commonly appears in the second and third decades of life. In 110 cases described by Paterson and McKissock,[14] 70 per cent developed their first symptom before the age of 30 years.

In 30 to 40 per cent of patients, unfortunately, the first signs will be those of intracranial hemorrhage, the majority with subarachnoid extension.[14-16] In such cases the diagnosis is made arteriographically. A bruit has been observed with as many as 50 per cent of angiomatous malformations, but is remarkably less common (9 to 12 per cent) when hemorrhage has occurred.[14, 16]

Spontaneous subarachnoid hemorrhage in a young patient suggests the diagnosis. Suspicion should be strong if there is a prior history of hemorrhage, epilepsy, or localized weakness. A bruit over the skull is confirmatory.

A single hemorrhage from an angiomatous malformation appears to carry a mortality of 10 to 20 per cent, much lower than the other causes of subarachnoid bleeding. However, bleeding frequently recurs over a period of years and each episode adds its risk of morbidity and death. Potter[13] has noted the course of 58 patients with this condition from less than 5 to more than 50 years (average 13 years) from the first symptom. In 38 patients treated conservatively there were 6 deaths from hemorrhage, all within 10 years of the first symptom. One other death resulted from hydrocephalus produced by the lesion. Eighty-two per cent of the entire group had 1 or more bleeding episodes during the follow-up. Over shorter periods of observation, other series show 30 to 60 per cent of patients to have had 1 or more hemorrhages at some time.[17]

If the malformation is surgically accessible, it may be excised, or if this is not possible, feeding vessels may be occluded. Surgical mortality at the present time is about 5 to 10 per cent for excision;[14, 15] Paterson and McKissock[14] report 16 cases wherein feeding vessels were occluded, with no deaths and good results. The location of the lesion is the prime factor influencing the surgical result. Cases must be carefully selected.

When hemorrhage causes an intracerebral hematoma with acute compressive symptoms, evacuation must be performed immediately.

Aneurysms

These lesions fall into 3 distinct groups: mycotic, as a result of softening of the arterial wall at the site of lodgment of a septic embolus; arteriosclerotic fusiform dilatations of the internal carotid, vertebral or basilar arteries; and congenital saccular, or "berry" aneurysms. The first group is rare and seldom causes subarachnoid hemorrhage. The arteriosclerotic variety also ruptures only rarely but produces neurologic signs and symptoms by pressing upon neighboring structures. The congenital saccular type occurs most commonly and ruptures most frequently. It is, therefore, with this group of aneurysms that we are primarily concerned.

The developmental fault leading to the formation of congenital aneurysms is not definitely known. Defects in the tunica media can be demonstrated at the points of bifurcation of the arteries at the base of the brain, which is the usual location of aneurysms. Such defects can also be found in patients without aneurysm. It has been postulated that congenital aneurysms may arise from remnants of the rich vascular network of the embryonic brain, a portion of which undergoes atresia during later stages of development. An increased incidence of aneurysm has been noted with other congenital defects such as polycystic kidney and coarctation of the aorta.[18]

Aneurysms are not uniformly dispersed throughout the circle of Willis and its branches. From a series of 1,023 cases,

McDonald and Korb[19] reported a distribution as noted in table 2. More than 1 aneurysm is found in 7 to 15 per cent of cases,[18, 20, 21] and as many as 5 have been found in the same patient.[18]

Hemorrhage from these lesions can occur at any age although it is most common between 30 and 60 years (fig. 1). In the unruptured state they may compress neighboring structures. One syndrome occurring after rupture is so diagnostic that it deserves special mention: sudden third nerve palsy (manifested by pupillary dilatation and oculomotor paralysis), when associated with the typical signs and symptoms of subarachnoid hemorrhage, is pathognomonic of bleeding from an aneurysm of the internal carotid artery at or near the origin of the posterior communicating branch.

Treatment of patients with saccular aneurysms is directed toward (1) prevention of rupture, (2) assisting the patient to overcome the immediate effects of hemorrhage, and (3) prevention of recurrent bleeding. To reach a conclusion concerning the wisdom and efficacy of any therapeutic regimen, the following facts relative to the "natural history" of the condition are necessary: A. What proportion of aneurysms rupture? B. What is the mortality and morbidity from initial hemorrhage? C. What is the probability of and the mortality and morbidity from recurrent hemorrhage? D. What is the most likely time for recurrent hemorrhage to take place? E. What are the effects of the age of the patient, the presence of hypertension and arteriosclerosis, and the size and location of the aneurysm on the factors listed above?

It is unfortunate that no absolute answers to these questions are available. Prior to the advent of angiography most aneurysms were discovered post mortem in patients who had died from their rupture. The era of angiography so quickly led to surgical intervention that the "natural course" described in current writings on this subject is often for patients adjudged too ill to withstand surgical attack.

TABLE 2.—*Distribution of Aneurysms in the Circle of Willis and Its Radicals as Noted by McDonald and Korb in 1023 Cases*[19]

Artery	Relative incidence (per cent)
Intracranial portion of internal carotid and its point of division	19
Anterior cerebral—anterior communicating complex	23
Middle cerebral	28
Posterior communicating	3.5
Posterior cerebral	3
Arteries of the posterior fossa	23.5

According to the figures presented by McDonald and Korb[19] from a study of 1,023 cases, approximately 77 per cent of aneurysms will eventually rupture. Thus the incidental finding of aneurysm in the living patient indicates a grave but not hopeless prognosis for longevity. For this reason we have recently advised no surgical therapy for a 70-year-old woman whose unruptured internal carotid aneurysm was producing facial pain.

The surgery of intracranial aneurysms is a comparatively new field. Carotid ligation was performed successfully in cases of "pulsating exophthalmos" (carotid-cavernous fistula) as early as 1808, but it was not until 1936 that Dandy[21] performed the first successful intracranial operation for nonfistulous aneurysm; concerted attack on these lesions has been carried out for the most part only since 1945. As with any new field of surgery, early results were frequently disappointing and the surgical mortality was high. Safer percutaneous angiography, the utilization of hypotension and hypothermia, and increasing surgical experience have, however, resulted in an improvement in the surgical outcome. In a recent series of 141 surgically treated patients operated upon by McKissock and Walsh[22] the over-all mortality was 33 per cent in contrast to 53 per cent deaths in their patients who were not operated upon. Norlen and Olivecrona[23] reported 78 patients operated upon with 10 deaths, a 13 per cent mortality. Jefferson and his co-

workers[24] subjected 142 patients with ruptured aneurysm to carotid ligation. There were 12 early and 8 late deaths, a mortality of 14 per cent. Poppen,[25] using several types of surgical approach, reports a mortality of 8 per cent in 226 cases.

It has been suggested, however, that the surgeons have chosen patients who have survived the high initial mortality and who would have lived if left alone. It becomes necessary, therefore, to examine such reports as have included the time interval from bleeding to operation and to compare these with a similar prognostic figure for conservatively managed patients seen at the same interval after hemorrhage.

We have mentioned the difficulty in obtaining an unselected series of angiographically proved aneurysms, observed without surgery, with which to compare the results of operation. McKissock and Walsh[22] reported a group of 108 such patients treated without surgery and followed from 6 months to 10 years after aneurysmal rupture. Bjorkesten and Troupp[26] reported a similar series of 40 cases. The basis for patient selection is not definitely stated for either series. It is nevertheless most interesting that a total mortality of 53 per cent was noted in the first series and a 55 per cent mortality in the second. These figures are in remarkable agreement with Walton's report of 55 per cent mortality within an average of 5 years of spontaneous subarachnoid hemorrhage where the cause of bleeding is unspecified, except for an attempt to exclude the hypertensive and arteriosclerotic group. From the literature to date it is not possible to construct a curve of progressive mortality for proved aneurysms conservatively managed after subarachnoid hemorrhage. However, since aneurysms produce about 80 per cent of subarachnoid hemorrhage as defined for Walton's series (fig. 2), and since the mortality after bleeding from aneurysm as derived from the data of McKissock and Walsh and Bjorkesten and Troupp would seem to correspond to that shown by Walton's series, figure 2 represents the best curve of mortality available for the study of aneurysms alone. It is probable, however, that Walton's series shows a higher early mortality (and therefore a lower mortality from recurrent bleeding) due to the inclusion of cases of spontaneous intracerebral hematoma. Also, as mentioned above, a number of Walton's patients had not been observed for a full 5 years after hemorrhage. In this respect, the mortality figures derived from Walton's report would seem to present the most optimistic picture of late mortality from recurrent subarachnoid hemorrhage due to ruptured aneurysm. We have adopted Walton's data for comparison with the results of operations for aneurysm in the opinion that it represents the most critical (if not the most accurate) standard available for such a comparison.

As a patient lives through successive days after the first subarachnoid hemorrhage, an increasing proportion of the statistical mortality is survived, and the mortality yet to be faced decreases. A curve of simple death rate (fig. 2) does not give a true picture of changing prognosis, since the mortality yet to be faced at any given time after the ictus must be absorbed by a steadily shrinking population. Walton's patients alive 1 week after the original hemorrhage had already lived through a 26 per cent population loss, and according to figure 2, 29 per cent of the entire population remained to die between 1 week and 5 years. But this 29 per cent toll now fell upon a population reduced to 74 per cent of the original, giving a mortality expectancy of 39 per cent for survivors at this point. Similar prognostic figures can be calculated from figure 2 for patients seen on any given day after the bleeding episode, and the prognostic curve formed by these points is shown in figure 4.

For comparison with prognosis on conservative management (fig. 4) there are, unfortunately, only a few surgical reports in which the operative mortality can be precisely determined for each interval from time of hemorrhage to time of surgery. A definite trend in the surgical results is nevertheless quite evident. Botterell et al.[20] reported 73

consecutive cases of ruptured aneurysm operated upon under hypothermia. Surgery was carried out in 44 within 1 week after the last episode of bleeding, and 16 of these patients died (36 per cent). Of the other 29 patients, 6 were operated upon 8 to 14 days after bleeding, and 23 thereafter, with no deaths. In the series reported by Norlen and Olivecrona,[23] 15 patients were operated upon within 3 weeks of bleeding, and 8 died. Of 63 patients operated upon 3 weeks or longer after the last hemorrhage, only 2 (3 per cent) died. It can be seen from figure 4 that in a similar group of patients not operated upon there is a 20 per cent chance of fatality within 5 years, even 8 weeks after the bleeding episode. All surgical procedures do not protect equally well against the possibility of recurrent hemorrhage, and adequate studies of the late results of aneurysmal surgery are lacking. It is probable, nevertheless, that obliteration of the aneurysms as reported above results in a "cure" if the patient survives the immediate postoperative period.

It is seen that at this writing very early surgery carries a mortality that may be higher than that for the natural history of the disease. This is due to the frequent presence of vasospasm, cerebral edema, and a severe neurologic defect in many of the patients undergoing surgery at this time. After a week or 2 have passed, vasospasm and cerebral edema have subsided and the patients with severe brain damage are dead. However, if this natural selection is allowed to operate until a time when surgery is completely safe, the fundamental purposes of surgery are defeated. If surgical intervention is to prevent the large morbidity and mortality from recurrence of bleeding in the second and third weeks (fig. 3), it must be performed before this time.

There is good evidence that the condition of the patient rather than a specific waiting period after bleeding should indicate the optimum time for intervention. Botterell et al.[20] noted that in 7 poor-risk patients, operated upon 4 hours to 7 days after bleeding, 3 died, 2 were classified as "bad results," and 2 as

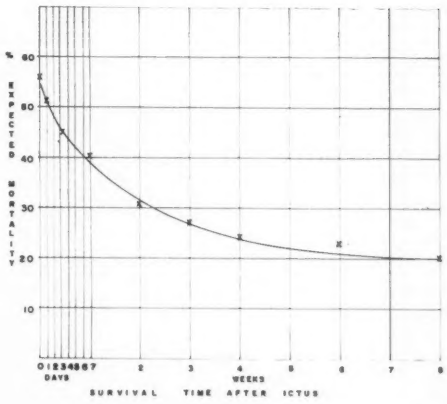


FIG. 4. Prognosis for patients with spontaneous subarachnoid hemorrhage based on figure 2. The survivors at any stated time after the initial hemorrhage are subjected to the indicated mortality risk for the remainder of a 5-year period. (Derived from Walton.[1])

"excellent." Four good-risk patients were operated upon 10 hours to 4 days after bleeding: 3 made "excellent" recoveries and 1 was classified as a "fair result." In the series of McKissock and Walsh,[22] there were 124 patients subjected to operation at an interval of less than 8 weeks from the last hemorrhage. Fifty-two patients were noted at the time of surgery to be comatose or semicomatose and to have "severe neurological signs." Thirty-four of these patients died (65 per cent). The remaining 72 patients operated upon during the same interval had "partly or completely recovered" from the effects of the first hemorrhage. In this group there was a 12 per cent mortality.

Thus the optimal time for early surgery is indicated by the patient's first improvement or stabilization following the hemorrhage. This clinical response is probably due to a reduction of cerebral edema and vasospasm, which are also important determinants of surgical mortality. We have found 2 criteria particularly helpful in deciding upon a time for surgery: the patient's state of consciousness and the degree of increased intracranial pressure as measured by lumbar puncture. For consistency in recording state of con-

sciousness, all patients are classified as alert (A), blunted (B), or comatose (C). Improvement or stability in category, coupled with falling or stable cerebrospinal fluid pressure, indicates the proper time for operation. As a rule, surgery is not performed if this pressure is greater than 220 mm. of water; in our experience a high pressure bodes ill for surgical intervention.

Once the patient has achieved the appropriate clinical state, surgery should be undertaken directly. Delay can offer only further opportunity for recurrence of hemorrhage, and a patient's good progress on one day is no guarantee against fatal rebleeding on the next.

Aneurysmal hemorrhage quite frequently results in secondary intracerebral hematoma. Five authors,[12, 18, 27-29] reported a total of 79 such instances in 204 cases of ruptured aneurysm—an incidence of 39 per cent. If signs indicate such a process with progression, immediate operation must be performed, regardless of the above factors.

Other considerations are also of prime importance to the outcome, whether management be conservative or surgical. McKissock and Walsh[22] noted a 47 per cent mortality among hypertensive patients subjected to surgery, while that for normotensive subjects was 26 per cent. For patients over 50 years of age, the mortality with surgery was 46 per cent; of the younger patients, 28 per cent died. Nearly identical differences in mortality were found for conservatively managed patients in the same categories. Furthermore, there is general agreement that both conservative and surgical prognosis will vary with the location and configuration of the aneurysm, but good statistical evidence is lacking at the present time.

The ideal operative procedure for aneurysm is occlusion of the aneurysmal neck by suture or clip, excluding the sac from the circulation without disturbance to circulatory dynamics. Unfortunately, some aneurysms are found to be nodular outpouchings, with no definite neck. Many are inaccessible to direct attack. Nearly all are tense and friable, and respond to enthusiastic manipulation with massive hemorrhage. A variety of procedures has been proposed and attempted in a large number of aneurysms varying widely in location and size. Clipping and ligation of the aneurysm neck, trapping procedures (occlusion of the feeding vessel on both sides of the lesion), muscle packing in and about the aneurysm, and cervical carotid occlusion are the most frequently described. We prefer an intracranial approach whenever possible, since in our opinion carotid ligation is not so certain to produce a permanently good result. Moreover, the sacrifice of one carotid artery in a younger patient would mean dire circulatory embarrassment if thrombosis of the second carotid artery should occur at a later date, and it has become increasingly evident that carotid thrombosis is an important cause of cerebrovascular accident in older patients. In some cases carotid ligation may be quite definitely preferable, and in some situations it may be the only procedure possible. One of us (H.T.B.) has recently performed such a ligation upon a 53-year-old woman who developed dysphasia and hemiparesis following hemorrhage from an aneurysm located in the terminal branching of the middle cerebral artery. It was considered that a direct surgical approach in this situation might increase the chances of permanent hemiparesis.

Angiography

It can be seen from the foregoing discussion that early angiography is an absolute necessity. Unless the exact size, shape, location, and nature of the offending lesion is determined, no rational plan of management can be formulated. The dynamics of collateral circulation, abnormalities of cerebral blood supply, and multiplicity of lesions must also be carefully considered before proper therapy can be instituted. Carotid injection should be done bilaterally whenever possible. Only a small proportion of aneurysms and anomalies are found in the vertebral-basilar portion of the circle of Willis, and these are usually not accessible to surgery. Because of this low yield and the difficulty of performing verte-

bral angiography, we believe that this procedure should be done only in special circumstances.

When bilateral carotid angiography fails to show a lesion, prognosis is relatively good and surgical intervention is usually precluded. Parkinson[30] reported 22 cases in which bilateral carotid angiograms were negative. None of these patients suffered a recurrence of bleeding during the subsequent 1 to 5 years. A similar group of 61 patients was observed by Bjorkesten and Troupp[26] for an average of 3 years. There were only 3 fatal recurrences (5 per cent). Angiography will miss a certain proportion (possibly 20 per cent) of aneurysms,[31, 32] especially if performed soon after hemorrhage. In some cases the presence of an aneurysm is suggested by vasospasm in the surrounding vasculature, and a later repetition of the study will demonstrate the lesion. Thrombosis within the aneurysm, developing after a bleeding episode, may prevent filling. The negative arteriogram in this circumstance still correctly indicates medical management and a relatively good prognosis.

The performance of cerebral angiography is not without its risk. With every large series of angiograms there is an occasional transient or permanent complication: hemiparesis, convulsions, internal carotid thrombosis, cervical trauma, and sensitivity to the injected contrast medium are reported. More rarely, death can result. However, as with the surgery in aneurysm, angiographic technic is steadily improving and these unfortunate complications are seen in decreasing number. In a recent series of 104 angiograms performed in this hospital there have been only 1 major complication and no deaths. When the tremendous mortality from undiagnosed and untreated subarachnoid hemorrhage is in the offing, carotid angiography seems well worth the risk.

Care of the Patient Who Has Recently Bled

In the comatose patient there is no substitute for a patent airway and adequate oxygenation, careful fluid balance, and prevention of urinary sepsis. Periodic observations of vital signs and state of consciousness should be recorded. The conscious patient should be kept at bed rest, and possible sources of exertion should be eliminated.

The recent development of hypothermia may prove of great value to the nonoperative management of these patients. With body temperature lowered to 30 C., the basal metabolic rate in human beings is reduced to about 60 per cent of normal.[33] In experimental dogs, Lougheed and Kahn[34] found a reduction of cerebral metabolic rate to between 23 and 35 per cent of normal when body temperature was lowered to 25 C., with no pathologic changes on sectioning the brain 6 months later. This reduction in cerebral metabolic rate will markedly lessen the damaging effects of local ischemia, as created experimentally[35] and as seen clinically.[29] Hypothermia is thus valuable in combating the ischemic effects of vasospasm and also appears to reduce cerebral edema. The use of prolonged hypothermia in the conservative treatment of acute bleeding has not yet been reported in a statistically significant number of cases; its ultimate place in conservative management is yet to be determined. Hypothermia is of particular value in the surgery of aneurysms, when carotid or vertebral blood flow must be occluded to facilitate the operation.[20, 29, 34]

Hypotensive agents have been used to reduce the danger of "rebleeding" in both conservative and surgical management. We think that the use of these agents is accompanied by a definite risk, however: the ischemic effect of local vasospasm is accentuated by a severe drop in blood pressure, and infarction is more likely to occur in those areas affected by vasospasm when hypotensive drugs are administered. The combination of hypotension and hypothermia would seem to be ideal from this point of view; unfortunately this combination is apparently conducive to cardiac arrhythmias, particularly ventricular fibrillation.[29] The future holds promise of greater use for these agents as their properties become better understood.

Summary and Conclusions

Spontaneous intracranial subarachnoid hemorrhage is an emergency, to be approached carefully but aggressively. If specific etiology is not established and appropriately attacked, more than half of the patients so afflicted will be dead, and only 1 in 5 well, within 5 years from the ictus.

Nearly all subarachnoid hemorrhage results from 1 of 4 basic conditions: intracranial aneurysm, angiomatous malformation, hypertensive-arteriosclerotic cerebral hemorrhage, and "spontaneous" intracerebral hematoma. A specific surgical approach in selected cases may considerably lower the mortality in each of these categories.

Because of the diagnostic, prognostic, and therapeutic significance of subarachnoid blood, lumbar puncture should be performed in all cases where intracranial vascular accident is suspected. If blood is found on lumbar puncture, bilateral carotid angiography should be performed as soon as possible, except in those cases in which a diagnosis of hypertensive hemorrhage can be clearly established on clinical grounds.

Evacuation of a rapidly expanding intracerebral hematoma is a simple, often life-saving procedure.

When hypertensive hemorrhage is excluded, the most common single cause of spontaneous subarachnoid hemorrhage is intracranial aneurysm. If the maximum number of patients with aneurysm is to be saved from fatal recurrent hemorrhage, definitive surgery must be performed at the earliest relatively safe time after the first hemorrhage. This time is found to coincide with the patient's earliest clinical improvement and stabilization. Immediate advantage should be taken of this improved state, since recurrence of hemorrhage may follow at any time. There can be no substitute for judgment and experience in choosing the proper course of action for each patient.

With continued clinical experience and rapidly advancing technics, such as hypothermia and hypotension, it is probable that an even greater saving of patients will soon be realized by surgery in the earlier period after bleeding.

Summario in Interlingua

Spontanee hemorrhagias intracranial subarachnoide representa un situation de urgentia que debe esser attaccate caute- sed agressivemente. Sie le etiologia specific non es identificate e attaccate per medios appropriate, plus que un medietate del patientes assi affligite va esser morte e solmente 1 inter 5 va esser ben al fin de 5 annos post le icto.

Quasi omne hemorrhagias subarachnoide resulta ab 1 de 4 conditiones fundamental: (1) Aneurysmo intracranial, (2) malformation angiomatose, (3) hemorrhagia cerebral hypertensive-arteriosclerotic, e (4) "spontanee" hematoma intracerebral. Un specific tactica chirurgic in seligite casos es forsan capace a reducer le mortalitate de maniera considerabile in cata un del mentionate categorias.

A causa del signification diagnostic, prognostic, e therapeutic de sanguine subarachnoide, un punctura lumbar debe esser effectuate in omne casos in que il existe le suspicion de un accidente vascular intracranial. Si le punctura lumbar revela le presentia de sanguine, angiographia carotic bilateral debe esser effectuate le plus promptemente possibile, excepte in casos in que un diagnose de hemorrhagia hypertensive pote esser establite clarmente super le base de datos clinic.

Le evacuation de un hematoma intracerebral a expansion rapide es un simple manovra que succede frequentemente a salvar le vita del patiente.

Post que le possibilitate de hemorrhagia hypertensive es excludite, le plus commun causa individual de spontanee hemorrhagias subarachnoide es aneurysmos intracranial. Si on vole salvar le plus grande numero possibile de patientes con aneurysma ab le effectos mortal de hemorrhagias recurrente, un definitive intervention chirurgic debe esser effectuate al prime momento post le hemorrhagia initial ubi illo es possible con libertate relative de hasardos. Il ha essite constatate que iste momento coincide con le tempore del prime melioration e stabilisation clinic del patiente.

Le opportunitate de un tal melioration debe esser utilisate immediatemente, proque un recurrentia del hemorrhagia pote sequer a non importa qual tempore. Nihil equivale judiciositate e experientia in le selection del melior curso de action pro le patiente individual.

Con le continuation del experientia clinic e le rapide progresso additional in le technicas applicabile—per exemplo hypothermia e hypotension—il es probabile que un procentage ancora plus alte de patientes va tosto poter esser salvate per intervention chirurgic promptemente post le sanguination.

REFERENCES

1. Walton, J. N.: Subarachnoid Hemorrhage. Edinburgh and London, E. S. Livingstone, Ltd., 1956, p. 350.
2. Tönnis, W.: Symptomatolgie und Klinik der supratentoriellen arteriovenosen Angiome. Premier Congres International De Neurochirurgie, Les Editions Acta Medica Belgica 205, 1957.
3. Adams, R. D., and Cohen, M. E.: Vascular diseases of the brain. Bull. New England Med. Center **9**: 180, 222, 261, 1947.
4. Odom, G. L., Bloor, B. M., Golden, J. B., and Woodhall, B.: Acute subarachnoid hemorrhage—etiology and mortality. North Carolina M. J. **13**: 624, 1952.
5. Ask-Upmark, E., and Ingvar, D.: A follow-up of 138 cases of subarachnoid hemorrhage. Acta med. scandinav. **138**: 15, 1950.
6. Hamby, W. B.: Spontaneous subarachnoid hemorrhage of aneurysmal origin—factors influencing prognosis. J.A.M.A. **136**: 522, 1948.
7. Hyland, H. H.: Prognosis in spontaneous subarachnoid hemorrhage. Arch. Neurol. & Psychiat. **63**: 61, 1950.
8. Magee, C. G.: Spontaneous subarachnoid hemorrhage—a review of 150 cases. Lancet **2**: 497, 1943.
9. Browder, E. S., and Corradini, E. W.: Surgical treatment of intracerebral hematomas. Arch. Neurol. & Psychiat. **65**: 112, 1951.
10. Ecker, A., and Riemenschneider, P.: Arteriographic demonstration of spasm of intracranial arteries, with special reference to saccular arterial aneurysms. J. Neurosurg. **8**: 660, 1951.
11. Margolis, G., Odom, G. L., Woodhall, B., and Bloor, B. M.: The role of small angiomatous malformations in the production of intracerebral hematomas. J. Neurosurg. **8**: 564, 1951.
12. Odom, G. L., Bloor, B. M., and Woodhall, B.: Intracerebral hematomas—a survey of 106 verified cases. Southern M. J. **45**: 936, 1952.
13. Potter, J. M.: Angiomatous malformations of the brain—their nature and prognosis. Ann. Roy. Coll. Surg. **16**: 227, 1955.
14. Paterson, J. H., and McKissock, W.: A clinical survey of intracranial angiomas, with special reference to their mode of progression and surgical treatment. Brain **79**: 233, 1956.
15. Olivecrona, H., and Riives, J.: Arteriovenous aneurysms of the brain. Arch. Neurol. & Psychiat. **59**: 567, 1948.
16. Mackenzie, I.: The clinical presentation of cerebral angioma. Brain **76**: 184: 1953.
17. Svein, H. S., Olive, I., and Angulo-Rivero, P.: The fate of patients who have arteriovenous anomalies without definitive surgical treatments. J. Neurosurg. **13**: 293, 1956.
18. Hamby, W. B.: Intracranial Aneurysms. Springfield, Ill., Charles C Thomas, 1952, p. 564.
19. McDonald, C. A., and Korb, M.: Intracranial aneurysms. Arch. Neurol. & Psychiat. **42**: 298, 1939.
20. Botterell, E. H., Morley, T. P., Lougheed, W. M., and Vandewater, S. L.: Hypothermia in the surgical treatment of ruptured aneurysms and carotid stenosis. Premier Congres International De Neurochirurgie, Les Editions Acta Medica Belgica 61, 1957.
21. Dandy, W. E.: Intracranial Aneurysms. Ithaca, N. Y., Comstock, 1945, p. 147.
22. McKissock, W., and Walsh, L.: Subarachnoid hemorrhage due to intracranial aneurysms—results of treatment of 249 verified cases. Brit. M. J. **2**: 559, 1956.
23. Norlen, G., and Olivecrona, H.: The treatment of aneurysms of the circle of Willis. J. Neurosurg. **10**: 404, 1953.
24. Jefferson, G.: Discussion of Norlen, G., and Falconer, M. A.: Proc. Roy. Soc. Med. **54**: 291, 1952.
25. Poppen, J. L.: Personal communication, 1957.
26. Bjorkesten, G., and Troupp, H.: Prognosis of subarachnoid hemorrhage. A comparison between patients with verified aneurysms and patients with normal angiograms. J. Neurosurg. **14**: 434, 1957.
27. Petit-Dutaillis, D., and Pittman, H. W.: Aneurysms of the middle cerebral artery: Report of seven operative cases; review of literature; evaluation of surgical therapy. J. Neurosurg. **12**: 1, 1955.
28. Graf, C.: Results of direct attack on non-fistulous intracranial aneurysm, with re-

marks on statistics. J. Neurosurg. **12:** 146, 1955.

29. Botterell, E. H., Lougheed, W. M., Scott, J. W., and Vandewater, S. L.: Hypothermia and interruption of carotid, or carotid and vertebral circulation, in the surgical management of intracranial aneurysms. J. Neurosurg. **13:** 1, 1956.
30. Parkinson, D.: The problem of spontaneous subarachnoid hemorrhage with proven aneurysms. J. Neurosurg. **12:** 565, 1955.
31. Walsh, L. S.: Subarachnoid hemorrhage. Acta Radiol. **46:** 321, 1956.
32. Kristiansen, K.: A clinical and radiologic evaluation of subarachnoid hemorrhage. Acta Radiol. **46:** 326, 1956.
33. Virtue, R. E.: Hypothermic Anesthesia. Springfield, Ill., Charles C Thomas, 1955, p. 62.
34. Lougheed, W. M., and Kahn, D. S.: Circumvention of anoxia during arrest of cerebral circulation for intracranial surgery. J. Neurosurg. **12:** 226, 1955.
35. Rosomoff, H. L.: Hypothermia and cerebrovascular lesions: I. Experimental interruption of the middle cerebral artery during hypothermia. J. Neurosurg. **13:** 332, 1956.
36. Rowley, J. F., Sullivan, J. F., and Tureen, L. L.: Spontaneous subarachnoid hemorrhage. Clinical and therapeutic factors affecting prognosis. Neurology **7:** 86, 1957.

Santos-Buch, C. A., Koenig, M. G., and Rogers, D. E.: Oral Treatment of Subacute Bacterial Endocarditis with Phenoxymethyl Penicillin (Penicillin V). New England J. Med. **257:** 249 (Aug. 8), 1957.

Observations on 6 patients with penicillin-susceptible streptococcal endocarditis who were treated with at least a 4-week course of large doses of penicillin V (2,000,000 units every 4 hours by mouth) and a streptomycin dihydrostreptomycin parenterally are presented. Clinical and bacteriologic cures were observed in all patients with no signs of relapse during follow-up periods ranging from 3 to 10 months. In 5 patients the serum penicillin levels were maintained above 1.6 units per ml. throughout the 4-hour interval between doses. Penicillin V serum levels, however, were consistently lower and less uniform than those obtained in other patients receiving equal doses of aqueous penicillin G intramuscularly, but were higher than those obtained with equal doses of penicillin G orally. Higher penicillin levels were found when the penicillin V was taken after meals. Simultaneous administration of aluminum hydroxide gel was found to depress the subsequent penicillin levels. Two patients developed nausea and vomiting of sufficient severity to interfere with therapy. One patient failed to obtain an adequate penicillinemia until probenecid was administered concurrently. Because the absorption of penicillin V taken orally is not predictable nor uniform enough to assure an adequate penicillinemia in this disease, the authors conclude that parenteral administration of penicillin still remains the preferred treatment for the majority of patients with subacute bacterial endocarditis.

Sagall

ABSTRACTS

Editor: STANFORD WESSLER, M.D.

Abstracters

DOMINGO M. AVIADO, JR., M.D., Philadelphia
GEORGE B. BROTHERS, M.D., Nashville
MASSIMO CALABRESI, M.D., West Haven
CHARLES D. ENSELBERG, M.D., New York
JOHN C. HARVEY, M.D., Baltimore
J. RODERICK KITCHELL, M.D., Philadelphia
SEYMOURE KRAUSE, M.D., Pittsburgh
GEORGE S. KURLAND, M.D., Boston
EUGENE LEPESCHKIN, M.D., Burlington
MORTON H. MAXWELL, M.D., Los Angeles
MORTON J. OPPENHEIMER, M.D., Philadelphia
ALFRED PICK, M.D., Chicago
SEYMOUR H. RINZLER, M.D., New York
WAYNE R. ROGERS, M.D., Portland
ELLIOT L. SAGALL, M.D., Boston
CHARLES R. SHUMAN, M.D., Philadelphia
LOUIS A. SOLOFF, M.D., Philadelphia
S. O. WAIFE, M.D., Indianapolis
MARTIN H. WENDKOS, M.D., Philadelphia

ATHEROSCLEROSIS

Asang, E., and Mittelmeier, H.: Systemis Endangiitis Obliterans. (Also a Contribution to the Pathogenesis of Arteriosclerosis.) Arch. Kreislaufforsch **26**: 143 (June), 1957.

Histologic and anatomic study of 75 patients with endangiitis obliterans shows that it affects many regions at the same time; the frequency of involvement in descending order is as follows: heart, aorta, kidneys, legs, spleen, intestines, liver, brain, stomach, pancreas, and lungs. Circulatory disturbances in the intestines, especially after operations, are among the major causes of death; 71 per cent of the patients were men, who may show the disease as early as the third decade, while women do not show it until the fifth decade of life. As the distribution is similar to that of thromboangiitis and atherosclerosis, all these abnormalities are considered to have a common origin—an initial increase of permeability of the endothelium for proteins, leading to their accumulation in the intima. When this is accompanied by marked inflammatory cell proliferation, the resulting marked stenosis causes rapid death, so that inflammatory changes are found to predominate at autopsy. When proliferation is slight, stenosis is insignificant and absorption of the protein exudate is incomplete, leading later to scarring and lipophanerosis, and finally to atheromatosis.

LEPESCHKIN

O'Reilly, P. O., Demay, M., and Kotlowski, K.: Cholesteremia and Nicotinic Acid. Arch. Int. Med. **100**: 797 (Nov.), 1957.

High blood levels of cholesterol may be important in atherogenesis. The authors used 1.0 Gm. of nicotinic acid orally 3 times daily in an attempt to lower elevated cholesterol levels. Three groups of patients were studied including a control group. The most commonly observed side reactions with the use of nicotinic acid were marked flushing and pruritus, which disappeared, however, after the first few days of treatment. In the dosage used, nicotinic acid consistently lowered the serum cholesterol values, and this effect seemed to be proportionate to the initial levels of the blood cholesterol. Nicotinic acid is said to operate as a normalizing, regulating, homeostatic agent for cholesterol, probably through the reticuloendothelial cells of the liver. The authors suggest 2 possible modes of action: a direct effect on the reticuloendothelial system of the liver in which there is an increased phagocytosis of the cholesterol by speeding up metabolic processes in these cells; and an indirect effect of nicotinic acid on lipids or neutral fats much as lipotropes are supposed to protect the liver. The authors even invoke the lipid clearing action of heparin by assuming that nicotinic acid may increase the metabolism of the mast cells and thereby increase the output of heparin.

KRAUSE

Kaplan, A., Jacques, S., and Gant, M.; Effect of Long-Lasting Epinephrine on Serum Lipid Levels. Am. J. Physiol. **191**: 8 (Oct.), 1957.

The injection of long-lasting epinephrine into dogs was followed in 1 hour by a rise in the concentration of serum triglycerides that was sustained for 24 hours. The concentrations of

serum lipid phosphorus and cholesterol, however, were not perceptibly altered for the first 6 hours after the injection, but were consistently elevated at the 24-hour period. Single injections of hydrocortisone, cortisone acetate or ACTH did not raise the serum concentration of lipid phosphorus or cholesterol in the 24-hour period after their injection. The triglyceride fraction did not rise significantly after cortisone or ACTH but did in some dogs receiving hydrocortisone.

WENDKOS

Gore, I., and Tejada, C.: The Quantitative Appraisal of Atherosclerosis. Am. J. Path. 33: 875 (Sept.-Oct.), 1957.

This article deals with a system devised by the authors for grading atherosclerotic plaques to bring some order into an evaluation of examinations of these lesions. The authors divide atherosclerotic lesions into 4 types in order of their pathologic importance. The first consists of lipid streaks, spots and patches in the aorta; the second consists of elevated, smoothly surfaced fibrous plaques of variable lipid content; the third consists of plaques of atherosclerosis with necrosis or hemorrhage, and the fourth of calcified plaques. These 4 types of lesions may be evaluated from examination of the surface area involved and weighted logarithmically, since physiologic processes of growth and degeneration have a semi-logarithmic relation. Utilizing this, the authors devised a theoretical index for atherosclerotic lesions. They think that if such standardizations were brought into the pathologic examination there would be a better understanding from one author to another. This information would be beneficial to an over-all study of atherosclerosis.

HARVEY

Tejada, C., and Gore, I.: Comparison of Atherosclerosis in Guatemala City and New Orleans. Am. J. Path. 33: 887 (Sept.-Oct.), 1957.

These authors, using a previously described index for evaluating atherosclerotic lesions in aortas, present a comparison of aortic lesions between 2 populations; the 1 in Guatemala and the other in New Orleans. The aortas from 616 unselected postmortem examinations done at the Charity Hospital in New Orleans and 320 unselected postmortem examinations done at the General Hospital in Guatemala City were studied. The examinations were performed without prior knowledge of age, sex, race, or cause of death. The atherosclerotic lesions were classified according to the index previously described. In both groups the atherosclerotic index shows a progressive rise with age. Under the age of 30 there was no significant difference between the 2 groups, but after the age of 30 the severity of atherosclerosis increased much more rapidly in the New Orleans than it did in the Guatemalan material. The authors submitted these differences in the atherosclerotic index to statistical evaluation and the difference appeared to be significant. Although the severity of the disease in the material from the 2 different populations was definitely related to age, there was a striking discrepancy in addition to age between the 2 sets of lesions. The Guatemalans with low incomes from whom the aortas were obtained have lower levels of blood cholesterol than Guatemalans with higher incomes, or than individuals from similar populations in the United States. Since the material in the study of the Guatemalan aortas came from those individuals of the low-income group, it is presumed that these individuals also had low levels of blood cholesterol, and that this perhaps caused the striking difference. A further study is being made to identify possible environmental factors responsible for these differences.

HARVEY

Duff, G. L., McMillan, G. C., and Ritchie, A. C.: The Morphology of Early Atherosclerotic Lesions of the Aorta Demonstrated by the Surface Technique in Rabbits Fed Cholesterol. Together with a Description of the Anatomy of the Intima of the Rabbit's Aorta and the "Spontaneous" Lesions which Occur in It. Am. J. Path. 33: 845 (Sept.-Oct.), 1957.

The usual way of sectioning and staining the aortas of rabbits fed cholesterol demonstrates focal lesions that consist of minute collections of large fat-filled cells immediately under the endothelium. With conventional methods of sectioning the earliest lesions are not demonstrated, and for this reason the authors have developed a technic of surface examination of the whole aortic intima mounted intact. Rabbits were fed a control diet, or a diet rich in cholesterol; the rabbits were sacrificed at appropriate times and the aortas mounted so that the surface technic examination could be carried out. A careful description of the mounting of the aorta to demonstrate the intact intima is presented. The anatomy of the normal endothelium, the intima, and the internal elastic membrane is well described.

There are focal lesions that appear in untreated rabbits. These always appear to be focal and consist of an acute inflammatory response in the intima and media, with exudation of polymorphonuclear leukocytes. There may be medial degeneration or a focal collection of cells of the monocytoid type packed densely together form-

ing a bulge into the aortic lumen. These cells do not contain stainable fat. In animals fed cholesterol the earliest atherosclerotic lesions were found 16 to 40 hours prior to sacrifice. There was very poor correlation between the duration of cholesterol feeding and the type of lesion produced. Again the atherosclerotic lesions demonstrated were always focal. In the very early lesions the only abnormality was the presence in the intima of droplets of fat stained with Sudan IV. Occasionally small lesions of a different type were seen. Collections of monocytoid cells containing fat droplets that lay immediately under the intact endothelium were seen rarely. In the cholesterol-fed rabbits the number of scattered monocytoid cells in the intima increased from 5 to 20 times. In the cholesterol-fed rabbit there sometims were increased numbers of other cells on the luminal surface of the endothelium. Most of these focal lesions occurred in zones in which the intima was normally thick, such as in the arch and the arterial mounds. Excellent illustrations are given with this article.

HARVEY

Wheeler, E. O.: Genetic Aspects of Atherosclerosis. Am. J. Med. **23**: 653 (Oct.), 1957.

The clinical features and mechanism of inheritance of hypercholesterolemic xanthomatosis were studied in 12 families. In families where 1 parent had hypercholesterolemic xanthomosis, 50 per cent of the children had hypercholesterolemia. In contrast, it was present in only 1 of 24 children from families where neither parent had the disorder. The observed familial prevalence was found to fit the pattern of simple Mendelian dominance. There was no evidence that the disorder was sex limited or that its prevalence was associated with birth order or any racial predilection. The appearance of xanthoma and coronary heart disease is dependent upon time and the severity of the lipid abnormalities.

KURLAND

Waters, L. L.: Studies on the Pathogenesis of Vascular Disease. The Effect of a Fatty Meal on the Course of Acute Inflammatory Lesions of the Coronary Arteries and Aortas of Dogs. Yale J. Biol. & Med. **30**: 101 (Nov.), 1957.

The author has reported previous observations that acute lesions can be produced in the coronary arteries of dogs by the use of epinephrine and other substances, and that these lesions can be modified by the intravenous injection of lipids. The present series of experiments were designed to test the effect of a single high-fat meal on the development of such lesions. During the alimentary hyperlipemia produced by a standard high-fat meal, repeated injections of epinephrine were given to maintain arterial pressures above 200 mm. for 30 minutes. No vascular lesions or lipid deposits occurred in the coronary arteries or aortas of dogs as a result of the high-fat meal alone. The lesions, developing in dogs receiving epinephrine alone, consisted of hemorrhage, edema, necrosis, and acute inflammation in the media, with no lipid deposits. However in dogs made hypertensive after a high-fat meal massive lipid deposits were found in the lesions which were not located differently than in the dogs receiving epinephrine alone. The accumulation of lipids began within minutes. This lipid did not exhibit a foam-cellular phagocytic reaction nor was it located subendothelially as in atherosclerosis in man. The lesions resembled more the medial changes of arteriolo-necrosis and arteriolosclerosis. The lipid remained extracellular, chiefly in droplet form, and disappeared progressively in 2 to 3 weeks. When heparin was given to clear the animals lactescant plasmas prior to inducing vascular injury, lipid deposits in the lesions were prevented. However, heparin given after inducing vascular injury did not prevent or modify the lipid accumulations. Presumably the lipid particles in the vessels did not possess the characteristics of chylomicrons, or the clearing factor in the plasma did not reach them.

ENSELBERG

Pick, R., Stamler, J., and Katz, L. N.: Effects of Hypothyroidism on Estrogen-Induced Inhibition of Coronary Atherogenesis in Cholesterol-Fed Cockerels. Circulation Research **5**: 510 (Sept.), 1957.

Hypothyroidism induced by thiouracil, thyroidectomy, or thyroidectomy plus administration of I^{131}, counteracted the ability of estrogens to prevent coronary atherosclerosis in cholesterol-fed chicks. This finding suggests that a euthyroid state is essential for effective estrogen antiatherogenesis. Although the mechanisms of this effect remain unclear, the results strongly reenforce fundamental concepts concerning pluriglandular influences on lipid metabolism and vascular architecture.

AVIADO

BLOOD COAGULATION AND THROMBOEMBOLISM

Haydon, G.B.: Electron Microscopic Observations of Blood Platelets and Fibrin Formation. Arch. Path. **64**: 393 (Oct.), 1957.

A rapid method for the examination of blood

platelets by electron microscopy is described, and selected electron micrographs from a series of blood samples are presented and discussed. The progressive enlargement of the platelets with increased clumping and disintegration observed by the author were interpreted as consistent with the concept of platelet destruction before clot formation. The platelets in preparations from the blood of a patient with pancytopenia were morphologically different from the platelets in all other preparations.

MAXWELL

Mayer, G. A., and Connell, W. F.: Control of Ethyl Biscoumacetate (Tromexan) Therapy by Standardized Clotting Time of Whole Blood. Canad. M. A. J. **77**: 930 (Nov. 15), 1957.

Tromexan was administered to 44 patients having mainly acute cardiac disease for a total of 930 treatment days. The therapy was of satisfactory intensity, as judged by finding the standardized clotting time (SCT) in the 15 to 20 minute range, on 72 per cent of treatment days in patients receiving a split dose (averaging 700 mg. per day) and in 45 per cent of treatment days in those on a single dose (averaging 880 mg. per day). This difference was attributed partly to the use in the former group of larger doses during the 4 or 5 days usually required to initiate therapy. No thromboembolic episode was noted during treatment and only 2 minor hemorrhages were seen. It was concluded that Tromexan is an excellent anticoagulant and that therapy with it is better guided by the SCT rather than by the more erratic 1-stage prothrombin determination.

ROGERS

Probstein, J. G., Joshi, R. A., and Blumenthal, H. T.: Atheromatous Embolization. An Etiology of Acute Pancreatitis. Arch. Surg. **75**: 566 (Oct.), 1957.

This report deals with 12 patients showing atheromatous embolization from the aorta to the pancreatic arteries, in 10 of whom there was an associated pancreatitis. The authors feel that acute pancreatitis of severity varying from mild acute interstitial inflammation to extensive parenchymatous and fat necrosis may be the result of obstructive vascular disease in the absence of any of the other etiologic agents to which this disease is usually attributed. Further, it is believed that the intensity of the parenchymatous reaction may be related to the number of pancreatic vessels involved in the embolic process. These observations are discussed in regard to the role of vascular factors in the genesis of acute pancreatitis. This report serves to point up certain considerations in the differential diagnosis in elderly patients presenting with symptoms of an acute intraabdominal process. Of particular importance is the differentiation between mesenteric thrombosis and acute pancreatitis, for surgery might be indicated in the former and contraindicated in the latter disorder. The increasing recognition of pancreatitis as a frequent complication of patients with cardiovascular disease points up the necessity of investigating, routinely, for possible pancreatitis in elderly persons.

BROTHERS

Olwin, J. H., and Koppel, J. L.: Practical Aspects of Long-Term Anticoagulant Therapy. Arch. Int. Med. **100**: 842 (Nov.), 1957.

Prothrombin depressants are usually used for long-term anticoagulant therapy, since the use of heparin is impractical. In spite of certain variables (including the use of thromboplastins which may contain factors V and VII thereby adding to the test system some of the very factors which are being assayed), the measurement of the prothrombin time is used to control drug dosage. The most widely used substances are coumarin derivatives or indandiones, which act in essentially similar ways but vary in the rapidity of the induction and recovery periods. Prothrombin levels are influenced by many factors among which are poor liver function, general nutritional state, diet, administration of other drugs, alcohol, patient cooperation, individual tolerance, and the experience of the clinician with the particular anticoagulant. The interval between prothrombin tests will depend upon the stage of therapy, the stability of the patient's prothrombin level, and to some extent on the particular drug used. Generally, at the start of therapy, prothrombin tests are obtained daily, and as the prothrombin time becomes reasonably stabilized within the therapeutic range longer intervals may elapse between tests. At no time, however, should this interval exceed 2 weeks. The effects of the anticoagulant drugs may require neutralization due to hemorrhage, trauma, or required surgery. Merely withdrawal of the drug may suffice frequently. If needed, however, vitamin K may be used; this may be particularly necessary with the longer acting anticoagulants, depending upon the amount of bleeding or urgency of the situation. The authors suggest that decontrol of anticoagulant effect be gradual in order to prevent thrombosis, as has been reported by others with sudden withdrawal of the drug. When it is anticipated that an anticoagulation effect may subsequently be required, supplementary intravenous heparin ad-

ministration may be used during the period when the prothrombin depressants are being neutralized or discontinued. Such an instance may occur when patients with atrial fibrillation and a previous history of embolism require surgery. In these situations the operative procedure required can be carried out safely at a prothrombin level of about 75 per cent; heparin, however, should be used until 4 hours prior to surgery. It is restarted along with the prothrombin depressant 6 hours after surgery and continued until the prothrombin time is again in the therapeutic range.

KRAUSE

CONGENITAL ANOMALIES

Mahaim, C., and van Nieuwenhuizen, C. L. C.: The Diagnosis of Ebstein's Disease. Five New Observations. Arch. mal. coeur **50**: 465 (May), 1957.

In the first 3 patients the typical findings of cyanosis and a very large heart, with decreased pulmonary blood content in the presence of complete or incomplete right bundle-branch block without electrocardiographic signs of right ventricular hypertrophy, were observed. In these patients the R wave even showed very low voltage or was absent in V_2 or V_3, corresponding to atrophy of part of the right ventricular wall. This enabled differentiation from pulmonary stenosis, where pulmonary blood flow is also reduced but the right ventricular hypertrophy pattern is always present, and from atrial septal defect, where the hypertrophy pattern is absent but the pulmonary blood flow is always increased. In the last 2 patients cyanosis was very slight and the cardiac configuration almost normal; however, the typical localization of pulsation to the pulmonary infundibulum was present. In these patients, the diagnosis was confirmed by the registration of 2 types of right ventricular pressure curves during cardiac catheterization (a high-pressure type corresponding to the small right ventricular cavity and a low-pressure type corresponding to the area under 1 of the rudimentary tricuspid valve leaflets). One of these patients showed a Wolff-Parkinson-White syndrome with type B configuration. This syndrome was found in 7 of 79 patients from the literature. Three patients showed a gallop rhythm over the right ventricle while angiocardiography disclosed an incisura in the shadow of the right ventricle corresponding to the displaced tricuspid valve. Angiocardiography is better tolerated than cardiac catheterization, which causes marked tachycardia and sometimes death.

LEPESCHKIN

Pappas, E. G., Mason, D., and Denton, C.: Marfan's Syndrome. A Report of Three Patients with Aneurysm of the Aorta. Am. J. Med. **23**: 426 (Sept.), 1957.

Three patients with Marfan's syndrome are presented with a description of the autopsy findings in 2. Generalized aneurysmal dilatation of the aorta with aortic insufficiency was present in all 3 patients. The basic pathologic lesion of the aorta was a cystic mucinous degeneration of the media. Autopsy showed a tear in the wall of the aorta without dissection in 1 patient; a second died during a surgical attempt to repair the aortic insufficiency; the third is still alive presumably having survived a dissecting aneurysm.

KURLAND

Kuhn, L. A., Lasser, R. P., and Gordon, A. J.: Hemodynamics of Patent Ductus Arteriosus: Analysis by Equisensitive Simultaneous Pressure Recording during Surgery. J. Appl. Physiol. **11**: 161 (Sept.), 1957.

Although there have been previous studies of aortic and pulmonary artery pressures in patent ductus arteriosus, the use of a single base line and identical sensitivities of the 2 manometric systems has not been employed previously for this purpose. The technic herein described is a useful adjunct to the surgeon not only to gage the extent of the change produced by surgery but also to help determine whether or not an additional lesion co-exists with the ductus. Detection of a murmur that cannot be explained by the existing pressure differential across the ductus should raise the strong suspicion of an additional lesion, the presence of which may be confirmed in some cases by failure of the pulmonary artery and aortic pressures to alter with temporary obliteration of the ductus. Should surgery be attempted in a case of reversed ductus, simultaneous equisensitive pressure recording ought to serve as a useful monitoring device to determine the changes produced by temporary, gradual obliteration of the ductus and thus aid in the decision as to whether or not the ductus should be permanently obliterated.

AVIADO

Agustsson, M. H., DuShane, J. W., and Swan, H. J. C.: Ventricular Septal Defect in Infancy and Childhood. Clinical and Physiologic Study of 19 Cases. Pediatrics **20**: 848 (Nov.), 1957.

This is a summary of the clinical and physiologic findings of cardiac catherization in 19 infants and children with ventricular septal defects. These 19 children varied in age from 3 months to 14 years. Eleven patients were female

and 8 were male. Thirteen came to operation. The usual physical examination and routine laboratory studies were done, including electrocardiogram, x-rays of the chest, and fluoroscopy. A detailed pattern is given of the interpretation of the electrocardiograms, and these are classified according to the authors' own system and analyzed in accordance with their defined terms as systolic, diastolic, and combined "overloading" of the ventricles. Extensive data are given from the results of the cardiac catheterizations and the dye-dilution studies performed at catheterization. The dye-dilution curves performed when the anesthetized subjects were breathing room air, or 100 per cent oxygen, showed distinct patterns, which could reliably indicate the direction of flow. In 17 of these 19 patients significant elevation of pulmonary arterial pressure was found. All exhibited a left-to-right shunt, but in addition significant right-to-left shunts were also encountered in all of the patients. The hemodynamic status of the patient may be difficult to evaluate when cardiac catheterization is carried out under anesthesia, because of its effect on ventilation. For this reason the dye-dilution studies to evaluate the shunts are mandatory when the cardiac catheterization is performed under anesthesia.

HARVEY

Scebat, L., Kremer, R., Voridis, E., and Clinckspoor, W.: The Effects of Effort upon Circulatory Hemodynamics in Congenital Malformations with Exclusive or Predominant Left to Right Shunt. Acta cardiol. **12**: 453 (Fasc. 5), 1957.

In 33 acyanotic cases of atrial septal defect, in 3 with a ventricular septal defect and in 12 with a patent ductus arteriosus, exercise on a bicycle produced the following hemodynamic changes: constantly an increase of the pulmonary arterial pressure and of the cardiac index as well as a decrease of the ratio pulmonary/peripheral flow; usually a decrease of the left-to-right shunt with reversal of the shunt in 2 cases of atrial septal defect; a considerable decrease of the peripheral arterial resistance as well as of the ratio peripheral/pulmonary arterial resistance. The authors attribute the variations in the direction of shunts following exercise to the alterations of resistances in the 2 circulations, rather than to changes of the pressure gradient between the communicating chambers.

PICK

Culbertson, J. W., Eckstein, J. W., Kirkendall, W. M., and Bedell, G. N.: General Hemodynamics and Splanchnic Circulation in Patients with Coarctation of the Aorta. J. Clin. Invest. **36**: 1537 (Nov.), 1957.

There is conflicting evidence regarding the hemodynamic patterns in patients with coarctation of the aorta. These authors studied the brachial and femoral arterial pressure, minute volume cardiac output, and hepatic portal circulation in 10 patients with coarctation. The data indicate that the hemodynamic pattern in coarctation is in sharp contrast to that observed in essential or renal hypertension. There was no increased resistance to blood flow out of the proximal aorta or through the kidney or in the splanchnic vascular bed in patients not in myocardial decompensation. Data indicate that peripheral resistance is grossly unequal in its distribution and resistance may be decreased or normal in vascular circuits both above and below the constriction in the same patient. This suggests that local regulatory mechanisms rather than a generalized vasoconstrictor influence are responsible for the distribution of peripheral resistance. Heart failure in 2 patients suggests a possible explanation for some of the discrepancies in previously published reports on isolated hemodynamic features of coaretation. The findings support a suggestion that the hypertension above the stricture is related to the degree of narrowing, or to a foreshortening of the aortic compression chamber, and to an increased stroke volume of the left ventricle. There is strong evidence against a renal mechanism in the genesis of the systemic hypertension of the upper compartment seen in this disease.

WAIFE

CONGESTIVE HEART FAILURE

Lindsey, A. W., Banahan, B. F., Cannon, R. H., and Guyton, A. C.: Pulmonary Blood Volume of the Dog and Its Changes in Acute Heart Failure. Am. J. Physiol. **190**: 45 (July), 1957.

Normal dogs were observed to have a pulmonary-left heart blood volume 13 per cent of total blood volume. In acute right heart failure secondary to pulmonary artery constriction the pulmonary-left heart blood volume was reduced 48 per cent below values in control animals. Acute left heart failure attendant on constriction of the ascending aorta produced an increase to 70 per cent above values established in normal control dogs.

OPPENHEIMER

Paul, O., Vawter, G. F., Schweitzer, A. W., and Hass, G. M.: Pathological Changes in Congestive Heart Failure. A Review of Findings in Fifty Cases. Arch. Path. **64**: 363, (Oct.), 1957.

A group of 50 patients with congestive heart

failure of 48 hours' or more duration were reviewed with a correlation of clinical and pathologic features. The latter were given chief emphasis in this description, and the range of gross and microscopic tissue changes were analyzed as to frequency and intensity of pathologic changes encountered. MAXWELL

Bourne, G.: A Study in Cardiac Prognosis. Brit. M. J. **2**: 851 (Oct. 12), 1957.

Not every case classified as a serious disease has a poor prognosis. The author cites individual cases to prove this point, rather than as a statistical guide. This is done to alert the clinician to analyze each situation in relation to the state of the myocardium and the determination of its deterioration or improvement at the time of the initial examination and on subsequent evaluation. This thesis is founded upon the fact that prognosis depends to a large extent upon the ability of the heart to maintain pumping efficiency. The normal heart does this at rest and can increase its efficiency concomitant with the demands of the daily activities. It is important, however, to be aware of the possibility that a previously diseased heart, now compensated, can often respond in a similar fashion for an undetermined period of time. KRAUSE

CORONARY ARTERY DISEASE

Lew, E. A.: Some Implications of Mortality Statistics Relating to Coronary Artery Disease. J. Chron. Dis. **6**: 192 (Sept.), 1957.

The author has studied mortality statistics and other data dealing with the trend of death rates from coronary artery disease. Variations in mortality from this disease by sex, race, marital status, geographic region, socioeconomic status and other factors are discussed. It was concluded that it is difficult to evaluate the real trend of mortality from coronary disease. The best that can be done from available mortality records is to make judicious estimates and to note where gross biases probably exist. The data analyzed furnish evidence that a number of factors are implicated in the increased death rate from coronary disease among white males.

MAXWELL

Forssell, J., and Brunila, T.: Cardiac Infarction and Pregnancy. Acta med. scandinav. **157**: 387 (June), 1957.

Cardiac infarction during pregnancy is extremely rare. In reviewing the available literature on this subject, the authors were able to find only 14 cases. To this number they have added 2 patients of their own that are reported in detail along with a study of all 16 patients. All patients, except 1, have been over 33 years of age and most have been multiparae. A previous history of hypertension, usually accompanied by angina pectoris, was present in all but 2 of the patients on whom sufficient data were available. Myocardial infarction occurred anywhere between the second and eighth months of pregnancy. In all instances where the patient was at least 7 months pregnant and the fetus viable, the mother survived parturition despite the infarction. There were 5 maternal and 7 fetal deaths. On the basis of this study, the authors are of the opinion that the occurrence of myocardial infarction in the mother does not necessarily constitute an indication for interrupting the pregnancy. BROTHERS

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, BALLISTOCARDIOGRAPHY, AND OTHER GRAPHIC TECHNICS

Runge, T. M., Oates, J. R., Herrmann, G. P., and Hejtmancik, M. R.: Extremely Rapid Arrhythmias and Regular Tachycardias in Parozysms in Patients with and without Accelerated A-V Conduction. Am. J. M. Sc. **234**: 170 (Aug.), 1957.

Premature activation of a part of the ventricular muscle by accelerated conduction of the excitatory impulse from the atria produces a characteristic electrocardiographic pattern of short P-R interval, slurred upstroke of R and a broadened QRS complex. This condition is prone to produce atrial tachycardia and atrial fibrillation. The development of paroxysmal atrial disorders may produce bizarre tracings with high ventricular rates simulating ventricular tachycardia. The diagnostic criteria set forth to distinguish the more benign arrhythmias are the presence of a P wave on every complex and the finding of short runs of supraventricular fibrillation with narrow QRS complexes between the pseudoventricular runs of complexes. Treatment of this condition with procaine amide in 0.25 to 1.0 Gm. doses given slowly intravenously with electrocardiographic monitoring has been effective in correcting the abnormal rhythm. Quinidine may be used if Pronestyl fails. It is emphasized that paroxysmal disorders, regular or irregular, with rates above 240 per minute are presumed to be due to the presence of accelerated A-V conduction. SHUMAN

Lissner, J.: Quantitative Electrokymography. Fortschr. Rontgenstr. **86**: 211 (Feb.), 1957.

The amplitude of the electrokymographic excursion is a function not only of the extent of the motion of the vascular or cardiac margin but

also of the brightness and the intensification of the fluoroscopic screen. In order to eliminate the latter 2 variables the author has devised a method of calibration that makes it feasible to correlate the shape of the electrokymogram quantitatively with the excursion of the vascular margin. This is accomplished by moving a frame through a known distance across the window of the photoelectric cell during diastole. In this fashion a calibrating excursion is registered on the electrokymogram analogous to the standardizing current on the electrocardiogram. The value of this method is illustrated by electrokymograms in the normal, in patients with calcareous pericarditis, and with mediastinal enlargement due to various causes. The author maintains that knowledge of the extent of pulsations of the mediastinal structures which is gained by this method is of help in differentiating vascular from transmitted motions.

SCHWEDEL

Richman, J. L., Wolff, L., and Call, R.: The Significance of QS Deflections in the Right-Sided Precordial Leads: Autopsy Correlation. Am. Heart J. **54**: 537 (Oct.), 1957.

The hearts of 55 patients in whom the electrocardiograms showed QS deflections in any one of the leads V_1, V_2, V_3, or V_{3R} were studied at autopsy. The high incidence of myocardial infarction (87 per cent) in the whole series indicates that QS deflections in right precordial leads are an important sign of myocardial infarction, but the absence of septal lesions in 29 per cent of the cases demonstrates that such deflections are not necessarily diagnostic of infarction of the interventricular septum. These electrocardiograms were further divided into 4 groups on the basis of the initial QRS deflections in V_e and V_6. In the group with rS deflections in V_e and R deflections in V_6, the pattern was not diagnostic of either septal or anteroseptal infarction but most probably represented complete or incomplete left bundle-branch block with myocardial infarction concealed by the pattern of left bundle-branch block. In the group with rS deflections in V_e and qR, qRs or QS deflections in V_6, infarction of the anterior wall was found in all cases, but involvement of the septum was not demonstrated histologically in over one third. In the group with QS deflections in V_e and qR deflections in V_6, a myocardial lesion was present in all but 1 case with extensive septal infarction. In the group with QS deflections in V_e and R deflections in V_6, an anterior wall lesion was present in every case, and in only 1 was the septum normal. The observations made thus indicate that QS deflections in 1 or more of the right-sided precordial leads are strongly suggestive of septal anterior wall infarction rather than infarction of the septum itself, providing left bundle-branch block can be excluded. An associated QS deflection in V_e tends to rule out left bundle-branch block and is, therefore, diagnostic, to a high degree of infarction of the interventricular septum. Although there was a positive correlation between the type of electrocardiogram and septal myocardial infarction, no specific fraction of the septum appeared to be crucial in the genesis of the electrocardiographic pattern of septal infarction.

SAGALL

Luisada, A. A., and Liu, C. K.: Simple Methods for Recording Intracardiac Electrocardiograms and Phonocardiograms during Left or Right Heart Catheterization. Am. Heart J. **54**: 531 (Oct.), 1957.

Two new technics are presented for use in routine cardiac catheterization or in special studies. Intracardiac electrocardiography is performed by using a column of 5 per cent saline solution with 10 per cent heparin within the catheter as an exploring electrode instead of a wire. With the limbs of the subject connected with the usual electrodes and the wire of an exploring electrode (chest lead wire) connected with the stop-cock of the strain gage, a unipolar intracardiac lead can be recorded by using Wilson's central terminal. Intracardiac phonocardiography is done by using a column of normal saline or glucose solution within the catheter as the carrier of sound waves. The electric output of the strain gage is differentiated, amplified, and filtered, and is recorded by a phonocardiograph. Application of these methods is simple and can be used routinely in animal or human catheterization, both in the right and left heart.

SAGALL

Sodi-Pallares, D., Brancato, R. W., Pileggi, F., Medrano, G. A., Bisteni, A., and Barbato, E.: The Ventricular Activation and the Vectorcardiographic Curve. Am. Heart J. **54**: 498 (Oct.), 1957.

The authors point out with experimental data how the vectorcardiogram may give valuable information on the sequence of ventricular activation. The sequence of ventricular activation may be recognized through a vectorcardiographic curve if the electric forces of 1 ventricle are markedly predominant (isolated ventricular hypertrophy, bundle-branch block, etc.). On the other hand, that information will be difficult to achieve if the magnitude of the electric forces are about the same for both ventricles (biventricular hypertrophy).

SAGALL

van Buchem, F. S. P.: The Electrocardiogram and Potassium Metabolism. Electrocardiographic Abnormalities in Primary Aldosteronism and Familial Periodic Paralysis. Am. J. Med. **23**: 376 (Sept.), 1957.

The electrocardiographic abnormalities arising from disturbances of potassium metabolism are illustrated by comparing the changes in a case of primary aldosteronism with those in familial periodic paralysis. In the former, when serum potassium was 1.7 to 2.8 mEq. per L. the electrocardiogram showed characteristic changes of lowering of the T wave, rise of the U wave and apparent prolongation of the QT interval. After subtotal adrenalectomy, serum potassium level returned to normal, but the electrocardiogram and acid-base and carbohydrate metabolism did not return to normal for several weeks. Although no paralysis occurred when the serum potassium was very low, it was observed when the serum potassium returned to normal. The data suggest a difference between myocardium and skeletal muscle in response to potassium depletion. On the other hand, during the attacks of periodic paralysis, in the second case, the electrocardiogram showed abnormalities characteristic of hypopotassemia.

KURLAND

Fletcher, E., and Brennan, C. F.: Paroxysmal Auricular Tachycardia with Auriculo-Ventricular Block. Brit. M. J. **2**: 792 (Oct. 5), 1957.

Paroxysmal atrial tachycardia with atrioventricular block is usually a complication of excessive digitalis administration. Although the presence of this arrhythmia may be suspected, it cannot be differentiated clinically from atrial fibrillation. The electrocardiogram must be inspected closely to detect the presence of pathognomonic P waves separated by isoelectric intervals. Treatment includes stopping the digitalis and conserving, as well as replacing, body potassium. Four cases properly diagnosed and treated are described. Continued digitalis administration in the presence of this arrhythmia (when produced by prior digitalis) may be disastrous. The authors, however, point out that this arrythmia may occur spontaneously. When this happens, the condition is apparently benign and paradoxically the use of digitalis is the treatment of choice.

KRAUSE

Henschel, E. O., Hamilton, L. H., and Rainbow, G. R. L.: Catheterization of Pulmonary Veins and Left Heart Chambers in the Dog. J. Appl. Physiol. **11**: 319 (Sept.), 1957.

An instrument has been developed that allows a needle to be guided through the carina into the preatrial sinus of dogs. From the preatrial sinus, it was possible to place the catheter into preselected lower pulmonary veins under fluoroscopic guidance. As in the transthoracic or transbronchial approach to the left atrium, there is some uncertainty associated with such a catheterization.

AVIADO

Moll, A. and Tummeley, G.: The Atrial Electrokymogram in Persons with Normal Hearts and in Patients with Mitral Disease. Arch. Kreislaufforsch. **26**: 217 (June), 1957.

The atrial electrokymogram was registered from 4 to 12 locations in the frontal and the 2 oblique positions in 20 normal persons and 23 patients with mitral disease. The curves were found to be most characteristic in the right anterior oblique position. Forty-three per cent of the 251 curves in normal persons showed a presystolic, a systolic, and a diastolic depression. In 24 per cent the systolic depression was poorly developed, and the beginning of the diastolic depression formed the apex of a cone. In 18 per cent the curve resembled a ventricular curve except for the prominent diastolic depression. In 11 per cent it resembled a pulmonary arterial curve as the nadir of the systolic depression was late. In 4 per cent a plateau preceded the diastolic depression; this form was found only near the pulmonary artery. In mitral disease this systolic plateau was found in 45 per cent, only in the presence of mitral regurgitation. The cone type of curve was found in 36 per cent, in all types of mitral disease. In these 2 types the systolic ascent began immediately after the first heart sound, in contrast to the same types in normal subjects, where it began late in systole. In 19 per cent a diastolic plateau was present, only in patients with pure or predominant stenosis; the plateau may show a notch corresponding to the beginning of the diastolic depression. If the diastole is short, the end of a systolic plateau may imitate a diastolic plateau.

LEPESCHKIN

Maier, C., and Spühler, H.: Observations in Sodium Lactate Treatment of Bradycardias. Cardiologia **31**: 325 (Oct.), 1957.

The effect of the intravenous infusion of 500 to 1000 ml. molar-sodium lactate was tested in 2 patients with Adams-Stokes attacks due to advanced A-V block and in 4 individuals with normal rhythm. In all instances a transient increase of the ventricular rate was induced, in the 4 normal individuals by acceleration of the sinus rate, in patients with second degree A-V block

by temporary restoration of 1:1 conduction, and in 1 instance of complete A-V block by production of runs of multifocal ventricular premature systoles. In all instances, molar lactate produced marked alkalosis with hypokalemia, slight reduction of calcium and chloride levels and an increase of sodium in the blood serum. The blood pressure did not change. Unwanted side effects occurred with the higher doses and consisted in restlessness, nausea, and tetanic manifestations.

PICK

Sciacca, A., and Sangiorgi, M.: Right Sided Intraventricular Conduction Disturbance Caused by a Lesion of the Common Bundle of His. (An Experimental Study.) Acta cardiol. **12**: 486 (Fasc. 5), 1957.

The authors were able to produce in 2 of 13 dogs a partial lesion of the common A-V bundle, which in the electrocardiogram was manifested by the appearance at first, of a transient complete A-V block, followed after restoration of A-V conduction by a constant right bundle-branch block. This observation is in keeping with a concept of Condorelli, which implies a functional dissociation of fibers for the right and left ventricle at the level of the common bundle. Applied to human pathology, this would mean that certain electrocardiograms considered to represent lesions in 1 of the bundle branches may in reality be caused by an incomplete lesion of the common bundle.

PICK

Kremer, R., and Delchevalerie, J.: Familial Cardiomegaly with Bundle Branch Block. Acta cardiol. **12**: 527, (Fasc. 5), 1957.

The authors report 3 siblings, 1 male and 2 females, 22 to 27 years old, with cardiomegaly of obscure origin. The electrocardiograms revealed in the first a typical complete left bundle-branch block, in the second a right bundle-branch block of the "rare" type, and in the third a pattern attributed by the authors to a bilateral incomplete bundle-branch lesion.

PICK

Fronêk, A., and Písâ, Z.: On the Fall of Blood Pressure in Acute Myocardial Ischemia. Arch. Kreislaufforsch. **27**: 34 (Sept.), 1957.

In 57 dogs the aortic pressure, the high frequency electromyogram (measuring the impedance between 2 epicardial electrodes on the anterior ventricular wall) and the electrocardiogram in a lead between these electrodes and in lead II were registered during occlusion of the anterior descending artery lasting 1 minute. The first signs of a systolic outward movement of the ventricular wall in the region supplied by the occluded artery appeared on the average of 3.51 seconds, while a decrease of blood pressure appeared on the average of 4.63 seconds after beginning of the occlusion. Elevation of the S-T segment and increased negativity of the T wave appeared after the beginning of the outward movement, while elevation of left atrial pressure appeared slightly before it. Vagotomy or novocaine infiltration of the ischemic region did not affect the sequence or magnitude of the fall of blood pressure. The incidence of this fall in pentothal anesthesia was 36 per cent while in chloralose anesthesia it was only 4.5 per cent; it became 80 per cent if an overdose of pentothal was given, and could be reduced 75 per cent after previous intravenous injection of calcium chloride. In was concluded that the decrease in blood pressure after myocardial ischemia of short duration was not due to a vagal reflex but to a direct depression of myocardial contraction, which was partly compensated by an increased force of contraction in the normal portion of the ventricle.

LEPESCHKIN

ENDOCARDITIS, MYOCARDITIS, AND PERICARDITIS

Saphir, O., and Cohen, N. A.: Myocarditis in Infancy. Arch. Path. **64**: 446 (Oct.), 1957.

The literature on isolated and virus myocarditis in infants and children was reviewed, and the clinical and pathologic findings were outlined. Five patients with myocarditis in infancy were recorded. Although no virus studies were made, it was believed by the authors that these were instances of viral etiology. An attempt was made to differentiate isolated (Fiedler's) myocarditis and viral myocarditis. Isolated myocarditis was predominantely an interstitial myocarditis, while in virus myocarditis, necrosis of isolated muscle fibers appeared characteristic.

MAXWELL

Aceves, S., Elizalde, R. A., and Luna, M. G.: Bacterial Endocarditis Superimposed on Syphilitic Aortitis. Arch. Inst. Cardiol. **27**: 231 (May-June), 1957.

Bacterial endocarditis usually develops on preexistent endocardial lesions, most commonly of rheumatic origin, or also on congenital malformations. A review of the literature shows that bacterial endocarditis superimposed on syphilitic lesions of the aortic valves is considered of rare occurrence by some authors. The purpose of this

presentation is to study the incidence of this association. The protocols of 1815 autopsies performed in the years 1944 to 1956 at the National Institute of Cardiology of Mexico were reviewed. One hundred cases of syphilitic mesoaortitis were observed: in 9 of these bacterial endocarditis was found: 2 of the 9 also showed rheumatic involvement of other valves. Forty-five cases of bacterial endocarditis were found among 476 patients with rheumatic disease of the aortic valves. It was concluded that bacterial endocarditis of the aortic valves was approximately as frequent in cases of syphilitic and of rheumatic aortic valvular disease. Clinical characteristics of the cases are presented. Two observations of bacterial endocarditis, apparently involving previously normal hearts, are briefly reported.

CALABRESI

Gilsanz, V., Vergara, A., and Estella, L.: Portal Circulation in Constrictive Pericarditis. A Study of the Spleen-Lung Ether Time in Relation to Splenoportography Before and After Pericardiectomy. Arch. Int. Med. **100**: 201 (Aug.), 1957.

In 2 patients with pericarditis with effusion and hepatomegaly, the spleen-lung ether time was found normal and the splenoportographic images showed no abnormality. On the other hand, the time that the contrast material remained in the portal system also coincided with that of normal subjects. In a patient with a pericardial effusion secondary to a neoplasm of the thymus with multiple metastases, the prolongation of the arm-lung time was related to the spleen-lung time, which was likewise prolonged. Thus in pericarditis with effusion there is no alteration that is not related to disturbances in other vascular territories. The authors believe that the spleen-lung ether time is a better method for determining the circulation time than is serial splenoportography. They conclude that the pathogenesis of the slowing of the circulation time is not the same in hepatic congestion as in constrictive pericarditis. In the first process there is a relation between the slowing of the portal circulation and the slowing in other venous territories. In the second case, obviously there must be an obstacle that, by means of the splenoportogram, is interpreted to be the sequel to the profuse fibrinous reaction over the surface of the liver. This obstacle is reversible after operation. In any case it is not possible to identify the splenoportographic images or the alterations of the circulation time in the region of portal vein in cases of hepatic congestion and in constrictive pericarditis.

BERNSTEIN

Hall, B.: Long-Term Follow-Up of Patients with Healed Bacterial Endocarditis. Ann. Int. Med. **47**: 880 (Nov.), 1957.

The present status of 17 patients who were discharged from the hospital cured of bacterial endocarditis 6 or more years was determined. During the first year after penicillin therapy 5 patients died, 3 of congestive heart failure and 2 of noncardiac causes. Two additional patients died 26 months and 6 years after penicillin therapy, of coronary heart disease and congestive failure, respectively. Of 10 living patients followed for from 6 to 10 years, 4 are asymptomatic, 5 have slight limitation of activity, and 1 is moderately disabled. Four of the 7 patients with aortic regurgitation are now dead, and the other 3 have shown a decrease in functional capacity. This finding contrasts with that for 9 patients who had only mitral valve disease, of whom 2 are dead, 3 have worsened symptomatically, and 4 are unchanged. One patient had the tetralogy of Fallot. This study shows that some patients may remain well for from 6 to 10 years after recovery from bacterial endocarditis, especially if aortic regurgitation is not present. Healed bacterial endocarditis must now be considered in the differential diagnosis of mitral regurgitation and of aortic regurgitation.

WENDKOS

HYPERTENSION

Gjol, N., Dybkaer, R., and Funder, J.: Shock in Phaeochromocytoma Treated with Noradrenaline. Brit. M. J. **2**: 673 (Sept.), 1957.

The case of a 77-year-old woman in whom the diagnosis of pheochromocytoma was confirmed by blood analysis during hypertensive crises and in whom these crises were followed by severe shock is reported. The shock was successfully treated with l-norepinephrine intravenously during 7- and 24-day periods.

SAGALL

Gray, I. R., and Hamer, N. A. J.: Protoveratrine A in Treatment of Hypertension. Brit. M. J. **2**: 609 (Sept. 14), 1957.

Protoveratrine A and B were shown to be effective hypotensive agents by the intravenous route, but oral administration of the 2 substances revealed a marked difference in their activity with much less potency of protoveratrine B by this route. Trials of protoveratrine A given in divided doses to a series of hospital in-patients showed it was possible to lower the blood pressure significantly in the majority without serious side effects, but the prolonged administration of the drug to a group of out-patients proved disappointing. In 17 out-patients so treated, the

effectiveness of the drug was limited by the development of unpleasant side-effects and in only 3 could the results be considered good. The authors concluded that in the somewhat limited group of patients who can tolerate an effective dose of this drug over long periods protoveratrine A had distinct advantages over other hypotensive agents. It should be considered for the treatment of patients with severe hypertension where oral therapy is preferred, especially those in whom treatment with ganglion-blocking drugs is not thought desirable.

SAGALL

Daniel, E. E., and Dawkins, O.: Aorta and Smooth Muscle Electrolytes During Early and Late Hypertension. Am. J. Physiol. **190**: 71 (July), 1957.

There is a significant potassium depletion in aortic and stomach smooth muscle in early desoxycorticosterone acetate (DCA) hypertension. There is some increase in sodium. No differences from normal controls were observed in aortas in post-DCA, renal or spontaneous hypertension of long standing. It is possible that the underlying changes in smooth muscle are different in early and late hypertension. Left ventricle and psoas muscle did not show changes like those of chronic hypertension.

OPPENHEIMER

Markelova, E. D.: Treatment of Latent Coronary Insufficiency in Hypertensive Disease by Means of Protective Inhibition. Klinich. Med. **35**: 119 (Sept.), 1957.

In 50 patients with the first and second phase of hypertensive disease the resting electrocardiogram was within normal limits, but after 30 knee bends in 30 seconds S-T depression of 1.8-2.0 mm., appeared in 15 patients. After a course of treatment by means of sleep induced as a conditioned reflex, S-T depression after exercise did not exceed 1 mm. in 14 of these 15 patients. All patients showed decrease of blood pressure and improvement of symptoms.

LEPESCHKIN

Zonenreikh, S.: Influence of the Higher Cerebral Centers on the Electrical Activity of the Heart. Klinich. Med. **35**: 68 (Sept.), 1957.

In 40 patients with arterial hypertension and 20 with hyperthyroidism orthostatic inversion of the T wave and depression of the S-T segment were more pronounced than in 30 normal persons. After a single dose of 0.2 Gm. of sodium amytal (oral) or 2.5 Gm. of chloral hydrate (rectal) the abnormalities of the T wave and the S-T segment in the resting and orthostatic electrocardiogram became less pronounced. This effect was greater with amytal than with chloral hydrate; it was usually accompanied by a slowing of the heart rate, but sometimes appeared without change of heart rate.

LEPESCHKIN

van Bogaert, A., Fannes, E., Tossetti, R., van Genabeek, A., Buytaert, L., Arnoldy, M., Vandael J., and van der Henst, H.: Long-lasting Experimental Pulmonary Arterial Hypertension in the Dog. Arch. mal. coeur **50**: 681 (Aug.), 1957.

In 19 dogs an anastomosis was created between the thoracic aorta and the left atrial appendage. If the anastomosis is too wide, the dog dies immediately with acute cardiac dilatation, or within 5 days in pulmonary edema. An anastomosis of 6 to 7 mm. is tolerated for many months. At first the systolic and diastolic pulmonary arterial pressures show moderate elevation; the capillary pressure is near diastolic arterial pressure but higher than left atrial pressure. This indicates a pulmonary venous spasm, accompanied soon by anatomic hypertrophy. The arterioles are distended. This phase favors pulmonary edema, thrombosis, and hemorrhage. After 4 or more months, the arterioles contract and show hypertrophy of the media; the arterial pressure is considerably elevated, exceeding the capillary pressure. In this way the venous system is protected. In the third phase the pulmonary arteries and veins develop degenerative changes. The left atrium shows considerable hypertrophy while the ventricles show predominantly right hypertrophy. The QRS complex shows right axis deviation through development of deep Q waves in lead I.

LEPESCHKIN

Roth, G. M., and Kvale, W. F.: Evaluation of Pharmacologic Tests as an Aid in Diagnosis of Pheochromocytoma: With Report of a Case of Pheochromocytoma and Tuberculosis. Dis. Chest **32**: 295 (Sept.), 1957.

The authors describe a 39-year-old man with extensive active tuberculosis who was complaining of severe headaches. The patient's responses to histamine and Regitine were positive and an exeretory urogram revealed a right suprarenal lesion. At operation a 52-Gm. pheochromocytoma was removed. Postoperatively, the patient's general condition improved, with relief of the headaches. The status of the pulmonary tuberculosis was unaltered.

MAXWELL

Comens, P., and Schroeder, H. A.: Intra-arterial Pressure in Man after Sudden Complete Occlusion as a Measure of Peripheral Resistance. J. Appl. Physiol. **11**: 181 (Sept.), 1957.

In 22 hypertensive patients, the brachial artery was occluded and the temporal course of the fall in pressure in the distal segment recorded. The rate of fall was regarded as a function of peripheral resistance, and this had a positive correlation with the diastolic pressure before occlusion. After hexamethonium ion injection, intravascular pressure after occlusion was not changed in any consistent way. No attempt was made to explain such a situation brought about by a known ganglion-blocking drug.

AVIADO

Bulle, P. H.: The Role of Certain Neuro-humors in Experimental Hypertension. Am. J. M. Sc. **234**: 329 (Sept.), 1957.

Arteriolar constriction may be due to the influence of the cerebral cortex acting upon the hypothalamus, which in turn may induce excessive sympathetic discharge. Neurohumoral factors released during cerebral activity may be conducted to the hypothalamus where a variety of reactions could be elicited, 1 of which is the excitation of vasoconstriction or increased adrenal medullary activity resulting in hypertension. To determine whether the hypothalamus responds to active agents contained in cerebrospinal fluid, dogs were injected in the subarachnoid space using acetylcholine, epinephrine, serotonin, or histamine. This procedure was followed after vagotomy, cervical ganglionectomy, adrenalectomy, ganglionic blockade with hexamethonium, and sectioning of the suboccipital spinal cord. It was found that acetylcholine was hypotensive whereas the other 3 agents elevated the blood pressure. After adrenalectomy, serotonin and histamine intracranially administered did not raise the blood pressure whereas epinephrine did. The results of these studies suggest that humoral stimulation of the hypothalamic centers play a role in "cerebrogenic" hypertension, that the superior cervical ganglia mediate the hypothalamic pressure impulses, and that the sympathetic adrenal medulla contains serotonin and histaminergic fibers.

SHUMAN

Cottier, P., Weller, J. M., and Hoobler, S. W.: Particular Aspects of Renal Excretion of Water and Electrolytes in Essential Hypertension. Cardiologia **31**: 278 (Oct.), 1957.

In 5 patients with normal blood pressure and 15 with essential hypertension of varying severity renal function tests (plasma flow, glomerular filtration and sodium, chloride, and potassium clearances) were studied subsequent to double loading with 0.9 and 2.5 per cent sodium chloride solutions. There were no changes during the infusions. In patients with slight and moderate hypertension an increase of diuresis and of electrolyte clearance took place pari passu with elevation of the blood pressure, apparently caused by a tubular mechanism. Contrariwise, in severe hypertension the sodium clearance fell with increasing renal resistance. Marked salt excretion was found in patients with moderate and severe hypertension with normal renal dynamics. On the other hand, normal or subnormal salt excretion occurred in slight hypertension, as well as in the patients with the highest blood pressures and markedly reduced renal blood flow. The authors conclude that water and salt excretion in patients with essential hypertension seems to depend on both the degree of pressure elevation and the state of renal hemodynamics.

PICK

Crandall, E. E., McCrorey, H. L., Sukowski, E. J., and Wakerlin, G. E.: Pathogenesis of Experimental Hypertension Produced by Carotid Sinus Area Constriction in Dogs. Circulation Research **5**: 683 (Nov.), 1957.

A persistent hypertension can be produced in dogs by bilateral constriction of the carotid sinus area. The 2 most likely possible causes for the hypertension are altered cerebral hemodynamics and absent or altered carotid sinus baroceptor function. The production of similar hypertension by bilateral constriction of the carotid branches above the sinus supports the concept of an alteration in cerebral hemodynamics. The acute effects of phenoxybenzamine and pentobarbital anesthesia are described but are not helpful in understanding the pathogenesis of hypertension.

AVIADO

Wyatt, G. M., and Felson, B.: Aortic Thrombosis as a Cause of Hypertension: An Arteriographic Study. Radiology **69**: 676 (Nov.), 1957.

Three patients with abdominal aortic thrombosis are presented. Each patient was normotensive and suddenly developed a marked elevation of blood pressure with severe hypertensive retinopathy. Translumbar arteriograms in each patient prior to and after the onset of hypertension showed retrograde propagation of the thrombus with partial obliteration of the circulation of 1 renal artery. Hypertension was relieved by the removal of the affected kidney. These patients demonstrate that the Goldblatt phenomenon of

hypertension following partial interruption of the blood flow to a kidney occurs in man. Appropriate arteriographic studies and surgery are curative. For this reason the condition should be kept in mind in any patient who suddenly develops severe hypertension and retinopathy.

KITCHELL

Clausen, E. G.: Pheochromocytoma in Children. Review of Significant Surgical Aspects and Report of Three Additional Cases. Am. J. Surg. **94**: 409 (Sept.), 1957.

Thirty cases of pheochromocytoma have been reported in children under 14 years. The author presents the case histories of 3 additional patients and emphasizes certain aspects of the diagnosis and treatment of these tumors gained from a review of all 33 cases. In 16 patients (48 per cent) the tumors were multiple. There were bilateral adrenal tumors in 8 (24 per cent) and extra-adrenal tumors in 7 (21 per cent). Although extra-adrenal tumors may be located anywhere in the body, there have been no reports of extra-abdominal lesions in children. The bifurcation of the aorta is the most common site for tumors of extra-adrenal origin. Failure of the blood pressure to fall after removal of 1 tumor suggests the presence of 1 or more additional tumors. The usual clinical manifestations of pheochromocytoma are seen and in many instances should be diagnostic. A particularly predominant manifestation in children is that of exceedingly moist, yet cold hands and feet, often with a bluish red discoloration. The patients are often malnourished, tense, and irritable with episodes of profuse nocturnal sweating. Radiologic examination of some type resulted in successful visualization of the tumor in 14 patients (42 per cent). Intravenous urography was helpful in 7 patients and perirenal air or oxygen in 7 of 13 patients, but this latter procedure produced severe reactions and had to be abandoned in 3 patients. The quantitative determination of catechols in urine as well as the determination of the effect of certain adrenolytic drugs on the blood pressure, were helpful in diagnosis. In the surgical removal of these tumors in children the transabdominal incision was the approach of choice. Regitine has been a valuable agent in the prevention of hypertensive crisis before and during operation, while epinephrine and norepinephrine have been useful in the control of postoperative hypotensive states. In bilateral adrenal lesions cortisone may be necessary. The over-all mortality was 54 per cent with an operative mortality of 44 per cent. With further development of methods of diagnosis and treatment these results should be improved upon.

BROTHERS

Muri, J. W.: Medical Therapy of Malignant Hypertension. Acta. med. scandinav. **158**: 173 (Sept. 6), 1957.

Five patients with malignant hypertension were treated with a combination of rauwolfia, hydralazine, and a new ganglionic blocking agent known as Oxaditon (bis-beta-trialky-l-ammoniumethyl ether halide). These patients were observed for 8 months to 1 year. In all 5 patients grade-IV changes were apparent in the eye grounds and 1 was in extremis with acute pulmonary edema secondary to left heart failure when treatment was instituted. Therapy was started with reserpine and a ganglionic-blocking agent given parenterally. A satisfactory reduction in blood pressure was obtained in all patients. Improvement of the retinopathy was striking. In 4 patients papilledema, soft exudates, and hemorrhages disappeared in a few weeks: 2 had normal eye grounds after 6 to 8 months of treatment. Two were left with eye grounds consistent with arteriosclerosis, and 1 patient, because of glaucoma, did not have a complete opthalmoscopic examination. Impaired renal filtration remained unchanged in 2 patients. No significant reduction in heart volume was observed. Four of the patients have resumed their previous occupations. The author favors combination therapy in malignant hypertension. The theoretical basis for combined therapy is the different mode and site of action of the hypotensive drugs that permit a potentiating effect; thereby smaller doses of the different preparations may be used, with a reduction of the side effects. Constipation was the most common side effect. None of the patients experienced syncopal episodes. In the author's experience, the combination of hypotensive drugs used, with Oxaditon as the ganglionic-blocking agent, was better tolerated than any single preparation of similar therapy with other hypotensive agents.

BROTHERS

Hollander, W., and Judson, W. E.: Electrolyte and Water Excretion in Arterial Hypertension. I. Studies in Non-Medically Treated Subjects with Essential Hypertension. J. Clin. Invest. **36**: 1460 (Oct.), 1957.

These authors have previously reported that abnormally high rates of sodium excretion follow the infusion of hypertonic saline in untreated patients with essential hypertension. In this study, the renal responses to the intravenous administration of 5 per cent sodium chloride solution in 8 normotensive subjects, 9 hypertensive subjects who had not been treated surgically, and 8 hypertensive subjects who had been treated with bilateral thoracolumbar sympathectomy are

reported. Metabolic and hemodynamic studies on these subjects indicate that both splanchnicectomized and nonsplanchnicectomized hypertensive individuals have an increased capacity to excrete sodium. This capacity was significantly correlated with systemic arterial pressure but not with renal plasma flow and glomerular filtration rate. The lack of a high degree of correlation between the level of blood pressure and the renal excretory response to infusion of a 5 per cent sodium chloride solution suggests that in addition to the pressure, other factors operate to enhance excretion. These may be the dietary intake, the extracellular fluid volume, the total body sodium, and adrenal cortical function.

WAIFE

METABOLIC EFFECTS ON CIRCULATION

Goldthwait, D. A.: Mechanisms of Synthesis of Purine Nucleotides in Heart Muscle Extracts. J. Clin. Invest. **36:** 1572 (Nov.), 1957.

Adenosinetriphosphate, ATP, is a key purine nucleotide involved in the conversion of chemical energy into mechanical work by myocardial tissue. This paper presents a study of the mechanisms of synthesis and degradation of purine nucleotides from in vitro studies of an extract of pig heart muscle. At present there are 3 known pathways for the synthesis of purine nucleotides. The first is the synthesis of the purine ring from small molecule precursors. The second is from the condensation of a free purine base with PRPP (5-phosphoribosylpyrophosphate). The third is through phosphorylation of a purine nucleotide. In the experiment reported, the more active synthetic pathways were via the phosphorylation of adenosine and the condensation of adenine or hypoxanthine with PRPP. De novo synthesis is less active. Enzymatic mechanisms are present for the synthesis and breakdown of nucleotides in heart muscle. The relation of the metabolism of nucleotides to cardiac function remains to be studied.

WAIFE

PATHOLOGY

Burdette, W. J.: Nucleotide Levels in Human Cardiac Muscle. Am. Heart J. **54:** 746 (Nov.), 1957.

Studies of human atrial muscle obtained as a biopsy at the time of cardiotomy revealed sufficient quantities of nucleotides to yield a fairly consistent quantitative picture. The distribution of the acid-soluble nucleotide fractions was similar for the myocardium of man, dog, and rat. The average amounts of adenosine monophosphate, adenosine diphosphate, and adenosine triphosphate were 6-6, 3-3, and 2.8 M $\times$ 10^{-4} per Gm., respectively. A number of other nucleotides were also present in the samples, suggesting that the adenosine system is not the only one involved in protein synthesis and energy transfers responsible for contraction of the human myocardium.

SAGALL

PHARMACOLOGY

Haeger, K., and Sjostrom, B.: Procaine Amide and Some Other Drugs in the Prevention and Treatment of Ventricular Fibrillation in the Hypothermic State in Rabbits and Dogs. Acta chir. scandinav. **113:** 167 (Aug. 22), 1957.

Studies were undertaken in rabbits to determine whether any substance would give protection against ventricular fibrillation in the hypothermic animal or would serve as a defibrillatory agent by itself or with electric defibrillators. Fibrillation was produced by electric stimulation, aconitine, or anoxia. Pronestyl reduced the incidence of fibrillation and increased the fibrillatory electrical threshold. Prostigmine, pyridostigmine, and chlorpromazine were ineffective. In manifest ventricular fibrillation in rabbits, Pronestyl arrested the fibrillation—possibly via ventricular flutter—and converted it to either cardiac arrest or sinus rhythm. A significant decrease in the frequency of fibrillation occurred in hypothermic dogs on whom cardiotomy was performed after Pronestyl. Electric or Pronestyl defibrillation was not made more difficult by prior administration of the other drugs studied.

KURLAND

Baker, J. B. E., Bentall, H. H., Dreyer, B., and Melrose, D. G.: Arrest of Isolated Heart with Potassium Citrate. Lancet **2:** 555 (Sept. 21), 1957.

Potassium citrate was tested as an arresting agent in 60 rabbit hearts and 4 human fetal hearts perfused by the Martin-Langendorff technic. When perfused with potassium citrate at concentrations of 2 mg. per ml., all hearts stopped in less than a minute, commonly in 10 to 20 seconds. During arrest, the myocardium was flaccid without escape or ventricular fibrillation. Recovery usually occurred within 15 seconds of the restoration of perfusion with Locke's solution and was maximal in 5 to 15 minutes. With arrest of coronary flow for only 15 minutes, recovery was only a little improved by previous arrest of the beat; but for 30-minute periods, previous arrest of the beat greatly improved recovery. Evidence is presented that potassium citrate is more

effective and less likely to provoke ventricular fibrillation than potassium chloride.

KURLAND

West, T. C., and Rushmer, R. F.: Comparative Effects of Epinephrine and Levarterenol (l-Norepinephrine) on Left Ventricular Performance in Conscious and Anesthetized Dogs. J. Pharmacol. & Exper. Therap. **120:** 361 (July), 1957.

The infusion of epinephrine or norepinephrine in unanesthetized dogs caused essentially similar effects on ventricular contractility. This observation confirms those of others using anesthetized dogs and isolated heart preparation. The difference in cardiac action of both amines reported by Goldenberg and his co-workers in human subjects remains unconfirmed by animal work, probably because of species differences.

AVIADO

Joos, H. A., and Johnson, J. L.: Digitalis Intoxication in Infancy and Childhood. Pediatrics **20:** 866 (Nov.), 1957.

This is a report of 10 instances of digitalis intoxication in 6 infants under 2 years of age, and in 4 children, the oldest being 8, which the authors encountered in their work at the Children's Hospital in Los Angeles. The family physician's prescription was responsible for overdigitalization in the majority of patients, although 1 was an error by the pharmacist in the preparation, and in another case miscalculation of a dose by a nurse was responsible for the poisoning. Vomiting and heart failure are the 2 chief clinical manifestations in these patients. Arrhythmias are a minor presenting symptom. Dehydration is a possible factor in contributing to digitalis poisoning. A great variety of electrocardiographic disturbances was found. The disturbances were commonly super-ventricular arrhythmias or changes in A-V conduction. It is emphasized that congestive heart failure may be a frequent manifestation of digitalis intoxication and cause some confusion in the elucidation of its actual cause when induced by over-digitalization. A plea is made for the use of more standardized products familiar to both physicians and pharmacists.

HARVEY

Holland, W. C.: A Possible Mechanism of Action of Quinidine. Am. J. Physiol. **190:** 492 (Sept.), 1957.

Quinidine increases the refractory period and depresses both the rate and amplitude of beat of isolated rabbit atria. These effects can be enhanced by elevating the potassium content of the medium 2-fold and completely blocked by lowering the potassium to one-sixteenth of the normal amount. Small amounts of acetylcholine act in a manner similar to potassium. These observations suggest that quinidine produces its effects by depressing the outward flux of potassium ions. Ion-transport studies revealed this to be the case. The hypothesis that quinidine in final analysis acts by blocking the intracellularly released acetylcholine is presented and discussed.

WENDKOS

Goldman, M. J.: Combined Quinidine and Procaine Amide Treatment of Chronic Atrial Fibrillation. Am. Heart J. **54:** 742 (Nov.), 1957.

Of 38 patients with chronic atrial fibrillation who could not be converted with quinidine alone, 50 per cent were converted to and maintained in a regular sinus rhythm with a combination of quinidine and procaine amide therapy. In most cases, the total dosage of the 2 drugs was less than that of quinidine alone. Less gastrointestinal toxicity was observed with the combination therapy than with the larger doses of quinidine. No serious toxicity resulted from the combined use of the 2 drugs. Following conversion, maintenance therapy with quinidine alone was possible in 15 of the 19 patients. The other 4 required quinidine and procaine amide in combination for maintenance of regular sinus rhythm.

SAGALL

Malbandian, R. M., Gordon, S., and Kaufman, J.: Calcium-Digitalis Tolerance Test, A Clinical Report of the First 24 Trials. Am. J. M. Sc. **234:** 391 (Oct.), 1957.

The calcium-digitalis tolerance test is based upon a synergistic relationship between calcium and digitalis upon myocardial irritability. The patient is given increasing increments of 10 per cent calcium chloride intravenously until an electrocardiographic endpoint is produced indicating toxicity. The signs of toxicity can be reversed by the administration of disodium ethylenediamine tetroacetate in appropriate dosage. In fully digitalized patients less calcium is required to produce an electrocardiographic endpoint and vice versa. In the absence of history, it is possible to determine the degree of digitalization and to calculate a complemental dose of digitalis required, if needed. The test is rendered safe by the use of the calcium chelating agent and by the normal plasma clearance of calcium. The test was performed in 15 patients with congestive heart failure and the calculations of the complemental doses of digitalis as cat units of the glycosides were presented. The electrocardiographic endpoints employed were bigeminy, wan-

dering pacemakers, and first degree heart block. Contraindications to the test were recent myocardial infarction, myocarditis, or angina pectoris. The test was indicated in any other patient in whom the adequacy of digitalization or the question of previous digitalis therapy needed to be determined.

SHUMAN

Benforado, J. M.: Studies on Veratrum Alkaloids. XXVI. Comparison of the Cardiac Action of Various Tertiary Amine Ester Alkaloids. J. Pharmacol. & Exper. Therap. **120:** 412 (Aug.), 1957.

The cardiac action (right atrial pressure, systemic outflow, average heart rate, and cardiac arrhythmias) of the tertiary amine ester alkaloids was studied after their administration by continuous infusion in the dog heart-lung preparation. The produced effects of veracevine, zygadenine, germine, and protoverine ester alkaloids were qualitatively similar to those reported for the cardiac glycosides. First noted was an action on cardiac contractility, followed by the onset of cardiac irregularities which terminated in ventricular fibrillation. These irregularities varied with the number and nature of the acids as well as with the nature of the alkamine, e.g., cevadine produced sinus tachycardia, veratridine and the other closely related zygadine esters produced ventricular premature contractions with bigeminy and ventricular tachycardia. The minimal lethal doses were in the range 1 to 30 μM per Kg. for all drugs tested except for cevadine (200 μM per Kg.). A significant relationship between lethal dose and rate of infusion was observed only for veratridine and veratroylzygadine. A significant inverse relationship between lethal dose and average heart rate was established for veratridine and vanilloylzygadenine.

RINZLER

Gotsch, K., Clodi, H., and Borkenstein, E.: Action of Myocardial Extract and Strophanthin on Circulatory Dynamics and Oxygen Consumption. Ztschr. Kreislaufforsch. **46:** 657 (Sept.), 1957.

In 4 patients with heart failure injection of an extract of bovine heart muscle caused a slight elevation of the blood pressure, heart output (method of Wezler and Böger), and oxygen consumption and a decrease of the calculated arteriovenous oxygen gradient. Injection of 0.125 mg. of strophanthin, alone or in combination with the extract, caused approximately the same changes. In 2 normal persons the injection caused only minimal changes.

LEPESCHKIN

Bär, C. G., and Bachmann, K.: Hemodynamic Studies with a New Ganglionic Blocking Agent (Camphidonium). Ztschr. Kreislaufforsch. **46:** 670 (Sept.), 1957.

Intravenous injection of 0.05 to 0.1 mg. camphidonium (methylated quaternary dimethylaminopropylcamphidine) per Kg. of body weight in 52 patients with hypertension but without heart failure caused a marked decrease of blood pressure, heart output, and stroke volume (method of Broemser and Ranke), lasting on the average 8, but sometimes up to 30 hours. The pulse-wave velocity and elastic arterial resistance did not show characteristic changes, while the tension period increased, especially in its component of rising pressure (interval from the first heart sound to beginning of carotid pulse). In 45 normotensive persons the effect was similar, except that tachycardia was much more pronounced and the diastolic pressure increased, so that the mean pressure remained unchanged.

LEPESCHKIN

Bellet, S., Finkelstein, D., and Gilmore, H.: Study of a Long-Acting Quinidine Preparation: Experience in Normal Subjects and in Patients with Myocardial Abnormality. Arch. Int. Med. **100:** 750 (Nov.), 1957.

Quinidine gluconate in a long-acting form was administered orally in a 1.0-Gm. dosage. It was demonstrated that a considerably slower decline in plasma quinidine concentration occurred with the use of this long-acting preparation. When its effects were compared with those in a control group receiving regular quinidine sulfate, the average peak concentration of blood quinidine was 4.34 mg. per L. at an average of 4.8 hours. In the following 4½ hours this level dropped at the rate of only 1 mg. per L. to a 12-hour concentration of 2.39 mg. per L., and a 24-hour concentration of 1.07 mg. per L. When given in 2 doses 10 hours apart (1.0 Gm. each) the plasma level was 3.81 mg. per L. 4 hours after the first dose, and 4.8 mg. per L. after the second dose. There was a gradual fall to 2.66 mg. per L. at 24 hours, and a concentration of 1.24 mg. per L. at 36 hours. When used in this dosage in 5 patients in congestive heart failure, the plasma levels achieved were even higher and longer sustained. Furthermore, with a similar dosage schedule, the efficacy of the long-acting quinidine preparation in abolishing extrasystoles, atrial tachycardia, and atrial fibrillation was similar to that of quinidine sulfate and occurred at comparable plasma levels.

KRAUSE

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N. Y.
Telephone Gramercy 7-9170

APPLICATIONS FOR AHA RESEARCH SUPPORT NOW BEING INVITED

Applications by research investigators for support of projects to be developed during the fiscal year beginning July, 1, 1959 are now being accepted by the Association.

The deadline for research fellowship applications and established investigatorships is September 15, 1958. Applications for grants-in-aid must be made by November 1, 1958.

Applications may be made for awards in the following categories:

Established Investigatorships: Awarded for periods of up to five years, subject to annual review, in amounts ranging from $6,500 to $8,500 yearly plus dependency allowance, to scientists of proven ability who have developed in their research careers to the point where they are independent investigators. In addition, a grant of $500 is made to the investigator's department to assist in defraying the expenses of his research program. Applicants for Established Investigatorships may apply for grants-in-aid to support their research at the same time they apply for Established Investigatorships.

Advanced Research Fellowships: Awarded for periods of one or two years to postdoctoral applicants who have had some research training and experience but who are not clearly qualified to conduct their own independent research. During the second year of tenure they will be permitted to spend up to 25 per cent of their time in professional and scientific activities not strictly of a research nature, providing that these will contribute to their professional development and do not involve services for a fee. These stipends range from $4,600 to $6,500 annually. Additionally, a grant of $500 is made to the investigator's department as in the case of Established Investigatorships.

Research Fellowships: A limited number of awards are available to young men and women with doctoral degrees for periods of one or two years to enable them to train as investigators under experienced supervision. Annual stipends range from $3,800 to $5,700. However, this type of award is primarily made by local Heart Associations.

Grants-in-Aid: Made to experienced investigators to help underwrite the costs of specified projects, such as equipment, technical assistance and supplies.

The Association also maintains another form of research support, the *Career Investigatorship.* This is given to a limited number of scientific investigators of unusual capacity and widely recognized accomplishment to assure them of financial support throughout their productive lives. Career Investigators are selected on the initiative of the Research Committee of the Association and *not by application.*

At least half of all funds received by the American Heart Association's National Office are allocated to research. Almost $31,500,000 has been allocated for research support by the Association and its state and local affiliates and chapters in the past 10 years.

Further information and application forms may be obtained from the Assistant Medical Director for Research, American Heart Association, 44 East 23rd Street, New York 10, N.Y.

EARLY REGISTRATION URGED FOR AHA SCIENTIFIC SESSIONS

As an inducement to early registration for attending the 31st Annual Scientific Sessions of the American Heart Association in San Francisco, October 24-26, all physicians who register *in advance* will receive for the first time this year an advance complimentary copy of the program booklet containing abstracts of the proceedings. Those registering

at the meeting will be required to pay $1.00 for the proceedings. Registration and accommodation forms are now available from the Association.

Following is a tentative schedule of the program:

Friday, October 24

The Scientific Sessions begin Friday morning. A morning session on genetics will be presented jointly by the Heart Association and the American Society for the Study of Arteriosclerosis. The Society is holding its Annual Meeting to coincide with the AHA Scientific Sessions this year for the first time. Sessions of general interest to physicians will also be held Friday morning under sponsorship of the AHA Councils on Circulation and on Cardiovascular Surgery.

A session sponsored by the Council on Rheumatic Fever and Congenital Heart Disease will be held Friday afternoon, as will a symposium conducted jointly by the Association's Council on Circulation and the Microcirculatory Conference. Friday evening's session will be on the subject of "Instrumental Study of the Heart and Circulation."

Practicing Physicians' Session

An all-day session for practicing physicians will be held concurrently on Friday under sponsorship of the Council on Clinical Cardiology. Presented last year for the first time, it is essentially a presentation of clinical problems in cardiovascular disease and has again been classified by the American Academy of General Practice as acceptable for Category II credit for Academy members.

Saturday, October 25

Scheduled for Saturday morning are a session on Applied Cardiovascular Research; the Lewis A. Conner Memorial Lecture by John H. Gibbon, Jr., M.D., Professor of Surgery, Jefferson Medical College, Philadelphia, on "Maintenance of Cardio-Respiratory Functions by Extracorporeal Circulation"; the George E. Brown Memorial Lecture by Lewis Thomas, M.D., Professor and Chairman, Department of Pathology, New York University College of Medicine, on "The Role of Hypersensitivity in Cardiovascular Disease"; and the presentation of the Albert Lasker Award of the American Heart Association for cardiovascular research.

On Saturday afternoon, joint Panels on "Emotional and Endocrine Aspects of Cardiovascular Disease" and "Effects of Hemodynamics and Vascular Injury" will be presented in conjunction with the American Society for the Study of Arteriosclerosis.

Sunday, October 26

The schedule for Sunday morning includes simultaneous sessions to be conducted by the Councils on Clinical Cardiology, High Blood Pressure Research, and Basic Science. A special program, "Rewards of Research," designed to interest laymen as well as physicians, will be held Sunday afternoon, as will a program on "Prevention of Rheumatic Fever." The Association's Annual Dinner is scheduled for Sunday evening.

In addition, the program will include the showing of a number of medical motion pictures. Also, a section of scientific and industrial exhibits will be provided. Plans are under way to present awards for the outstanding scientific exhibits on display.

The Annual Meeting of the Assembly to review national policies and activities of the Association will be held on Monday, October 27 and Tuesday, October 28 at the Hotel Fairmont. The Assembly convenes on Monday morning to hear a keynote address by William P. Shepard, M.D., 2nd Vice President, Health and Welfare Division, Metropolitan Life Insurance Company.

Six Assembly Panels will be in session on Monday. They will discuss the following subjects: Research; Fund Raising and Public Relations; Relationships and Responsibilities Between National, State and Local Heart Associations; Community Service—Screening and Case Finding Programs; The Physician's Continuous Self-Education; and Membership.

The general session of the Assembly meets on Tuesday morning to review Panel recom-

mendations and elect officers and Board members of the Association.

Deadline for Abstracts is June 13

June 13, 1958 is the deadline for submission of abstracts of scientific papers to be selected for presentation at the Scientific Sessions. Applications for space for scientific and industrial exhibits must also be submitted by June 13.

HAWAII SCIENTIFIC SESSIONS

The Hawaii Heart Association has invited physicians and scientists to participate in two-day scientific sessions and a tour of the Islands following the AHA Scientific Sessions in San Francisco. Attendance may be arranged through H. Douglas Chisholm, Associate Director, American Heart Association, 44 East 23rd Street, New York 10, N.Y., or directly through the American Express Company, 65 Broadway, New York, N.Y.

ASSOCIATION NOW A SPONSOR OF THE "HEART BULLETIN"

The "Heart Bulletin," a bimonthly journal on cardiovascular disease for the practicing physician, is now sponsored by the American Heart Association in cooperation with the National Heart Institute and the American Academy of General Practice. The new sponsorship began with publication of the May, 1958 issue.

Since its initiation in 1952 as a public service by the Medical Arts Publishing Foundation of Houston, the publication has covered a wide range of subjects in the cardiovascular field of particular interest and use to physicians in general practice. The Foundation will continue publication and distribution of the "Bulletin."

Under its new sponsorship, seven Associate Medical Editors have been appointed by the Heart Association to assist Dr. Russell W. Cumley, who remains as Executive Editor. The new associate editors and their respective fields of specialization are:

Sidney Blumenthal, M.D., New York City, Pediatrics; Harriet Dustan, M.D. Cleveland, Research; Dr. Edward D. Freis, Washington, D. C., Hypertension; John W. Kirklin, M.D., Rochester, Minn., Cardiovascular Surgery; Arthur J. Merrill, M.D., Atlanta, Peripheral Circulation; Gerald H. Whipple, M.D., Boston, Electrocardiography; and James V. Warren, M.D., Durham, N.C., Clinical Cardiology.

HYPERTENSION PROCEEDINGS ARE NOW AVAILABLE

The Proceedings of the Annual Meeting last November of the Council on High Blood Pressure Research are now obtainable through the American Heart Association, 44 East 23rd Street, New York 10, N.Y., or through local Heart Associations at $2.50 a copy. The volume, which contains an up-to-date symposium on mineral metabolism as related to arterial hypertension, is the sixth in a series on Hypertension based on the Council's annual meetings.

LOW-COST ACCOMMODATIONS ARRANGED AT WORLD CARDIOLOGY CONGRESS

Arrangements have been made by the Organizing Committee of the Third World Congress of Cardiology for residents, research fellows and young physicians who attend on limited budgets to be accommodated at the Ville Universitaire de Louvain at approximately $2.00 nightly including continental breakfast. Transportation facilities to and from Brussels, about 20 miles distant, will be provided.

Such accommodations may be arranged by writing to Dr. Fr. van Dooren, Secretary of the Congress, 80 rue Mercelis, Brussels. A check representing the total sum for the number of nights anticipated should be included. Checks should be made payable to: Third World Congress of Cardiology, account No. 90.490 at the Banque de la Societe Generale de Belgique, 3 Montagne du Parc, Bruxelles (Belgique).

WORLD CARDIOLOGY CONGRESS ROUND-TABLE SUBJECTS LISTED

Physicians and scientists from all over the world will participate in a variety of symposia and round-table discussions in addition to

presenting many papers at the Third World Congress of Cardiology in Brussels, Belgium, September 14-21.

Subjects for the Round-Table sessions include: Surgery of Congenital Heart Diseases; Surgery of Acquired Heart Diseases; Chronic Pulmonary Heart Diseases; Cardiac Insufficiency; Angina Pectoris and Myocardial Infarction; Rheumatic Fever; Clinical Significance of Minor Electrocardiographic Alterations; Subacute Bacterial Endocarditis; Peripheral Vessels; Angiocardiography; Phonocardiography; and Pulmonary Function in Mitral Stenosis.

Subjects for the Symposia were listed in the May, 1958 issues of *Circulation* and *Circulation Research*.

RHEUMATIC FEVER MEETING PROCEEDINGS AVAILABLE

Proceedings of a national meeting on secondary rheumatic fever prevention programs, co-sponsored by the American Heart Association and the U. S. Public Health Service, March 9-11 in Chicago, are now available to interested physicians by request from the American Heart Association or local Heart Associations.

MEETINGS CALENDAR

June 21: International Cardiovascular Society, North American Chapter, San Francisco. Henry Haimovici, M.D., 105 East 90th Street, New York 28, N.Y.

June 23-27: American Medical Association, San Francisco. George F. Lull, 535 N. Dearborn, Chicago 10, Ill.

August 11-14: National Medical Association, Milwaukee. John T. Givens, 1108 Church Street, Norfolk 10, Va.

August 24-29: Congress of Physical Medicine and Rehabilitation, Philadelphia. Frances Baker, 1 Tilton Street, San Mateo, Calif.

October 6-10: American College of Surgeons, Chicago. Michael L. Mason, 40 E. Erie Street, Chicago 11, Ill.

October 24-28: American Heart Association 31st Annual Scientific Sessions, San Francisco. American Heart Association, 44 East 23rd Street, New York 10, N.Y.

October 27-31: American Public Health Association, St. Louis. Berwyn F. Mattison, 1790 Broadway, New York 19, N.Y.

October 31-Nov. 1: Central Society for Clinical Research, Chicago. A. S. Weisburger, 2065 Adelbert Road, Cleveland 6, Ohio.

ABROAD

June 15-19: Canadian Medical Association, 91st Annual Meeting, Halifax, Nova Scotia. Canadian Medical Association, 244 George Street, Toronto 5, Canada.

August 15-20: World Medical Association, Copenhagen, Denmark. Louis H. Bauer, 10 Columbus Circle, New York 19, N.Y.

September 14-21: Third World Congress of Cardiology, Brussels. Dr. F. Van Dooren, 80 Rue Mercelis, Brussels, Belgium.

September 22-28: 16th International Congress of History of Medicine, Montpellier, France. Louis Dulieu, M.D., Montpellier, (Herault) France.

September 25-28: Third International Congress of Angiology, Venice, Italy. M. Comel, M.D., Dermatological Clinic, University of Pisa, Pisa, Italy.

CONTRIBUTORS TO THIS ISSUE

J. A. Abildskov, M.D.

Assistant Professor of Medicine, State University of New York, Upstate Medical Center, Syracuse, N.Y.

Herbert L. Abrams, M.D.

Associate Professor of Radiology, Stanford University School of Medicine, San Francisco, Calif.

Murray C. Arkin, M.D.

Formerly, Resident in Internal Medicine, Medical Service, Veterans Administration Hospital, Hines, Ill.

H. Thomas Ballantine, Jr., M.D.

Associate Visiting Neurosurgeon, Massachusetts General Hospital, and Clinical Associate in Surgery, Harvard Medical School, Boston, Mass.

Lionel M. Bernstein, M.D., Ph.D.

Assistant Director, Professional Services for Research, Veterans Administration Hospital, Hines, Ill.; Attending Physician, Cook County Hospital; Associate, Department of Medicine, University of Illinois, College of Medicine, Chicago, Ill.

John W. Berry, M.D.

Assistant Professor of Internal Medicine, St. Louis University School of Medicine, St. Louis, Mo.

B. M. Bloomberg, M.D.

Honorary Lecturer, Department of Pathology and Microbiology, University of the Witwatersrand, Johannesburg, South Africa.

Bernard Blumberg, M.D.

Formerly, Resident in Internal Medicine, Medical Service, Veterans Administration Hospital, Hines, Ill.

Frank Burno, M.D.

Formerly, Resident Physician, Medical Service, State University of New York, College of Medicine, Downstate Medical Center, Brooklyn; Kings County Hospital, Brooklyn, N. Y.

Robert B. Case, M.D.

Senior Assistant Surgeon, Laboratory of Cardiovascular Physiology, National Heart Institute; Presently, St. Luke's Hospital, New York, N. Y.

William D. Cohen, Ph.D.

Chief Research Biochemist, The Research Laboratory, The Memorial Hospital, Worcester, Mass.

Jesse E. Edwards, M.D.

Consultant, Section of Pathologic Anatomy, Mayo Clinic; Professor of Pathology, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

Robert H. Furman, M.D.

Head of the Cardiovascular Section and Associate Director of Research, Oklahoma Medical Research Foundation; Associate Professor of Research Medicine, University of Oklahoma School of Medicine, Oklahoma City, Okla.

Benjamin M. Gasul, M.D.

Chief, Pediatric Cardiac Service, Cook County Children's Hospital, Chicago, Ill.

E. Richard Halden, M.D.

Instructor, Internal Medicine, University of Texas Southwestern Medical School, Dallas, Tex.

Norio Higano, M.D.

Member, The Research Laboratory, Chief, Radioisotope Laboratory, and Endocrinologist, Medical Division, The Memorial Hospital, Worcester, Mass.

R. Palmer Howard, M.D.

Head of the Endocrinology and Metabolism Section, Oklahoma Medical Research Foundation; Associate Professor of Research Medicine, University of Oklahoma School of Medicine, Oklahoma City, Okla.

Richard Imagawa, M.D.

In private practice, Santa Ana, Calif.

Edward J. Jahnke, Jr., Maj., MC

Former Chief of Thoracic Surgery, Walter Reed Army Hospital, Washington, D. C.

Robert L. Johnson, Jr., M.D.

Instructor, Internal Medicine, University of Texas Southwestern Medical School, Dallas, Tex.

E. Corinne Keaty, Ph.D.

Formerly, Member, Endocrinology and Metabolism Section, Oklahoma Medical Research Foundation. Presently, Department of Obstetrics and Gynecology, Louisiana State University School of Medicine, New Orleans, La.

David M. Klein, M.D.

Clinical and Research Fellow in Neurosurgery, Massachusetts General Hospital, Boston, Mass.

F. Lazarus, B.Sc.

Clinical Laboratories, Medical Centre, Johannesburg, South Africa.

James J. Leonard, M.D.

Trainee in Cardiology, National Heart Institute, U. S. Public Health Service; Instructor in Medicine, Duke University, Durham, N. C.

James P. Lillehei, M.D., M.S.

Instructor, Internal Medicine, University of Texas Southwestern Medical School, Dallas, Tex.

Harold A. Lyons, M.D.

Associate Professor of Medicine, State University of New York, College of Medicine, Downstate Medical Center, Brooklyn, New York; Director of the Second Pulmonary Disease Division, Kings County Hospital, Brooklyn, N. Y.

William C. Manion, M.D.

Chief, Cardiovascular Pathology, Armed Forces Institute of Pathology, and Central Laboratory for Pathological Anatomy and Research, Veterans Administration, Armed Forces Institute of Pathology, Washington, D. C.

Thomas W. Mattingly, Brig. Gen., MC

Chief, Department of Medicine and Chief of Cardiology Service, Walter Reed Army Hospital, Washington, D. C.

James Metcalfe, M.D.

Associate Physician, Boston Lying-in Hospital; Associate in Medicine, Harvard Medical School, Boston, Mass.

Andrew G. Morrow, M.D., F.A.C.S.

Chief, Clinic of Surgery, National Heart Institute, Bethesda, Md.

Irene Mrost, B.A.

Clinical Laboratories, Medical Centre, Johannesburg, South Africa.

John O. Nestor, M.D.

Consultant in Pediatric Cardiology, National Heart Institute, Besthesda, Md.

Loren F. Parmley, Lt. Col., MC

Assistant Chief, Cardiology Service, Walter Reed Army Hospital, Washington, D. C.

Hubert V. Pipberger, M.D.

Instructor in Medicine, Georgetown University, School of Medicine, Washington, D.C.

Thomas C. Roach, M.D., Capt., U.S.A.F.

Lockbourne Air Force Base, Columbus, Ohio.

Roger W. Robinson, M.D.

Director, The Research Laboratory; Cardiologist and Chief, Medical Division, The Memorial Hospital, Worcester, Mass.

Saul J. Robinson, M.D.

Associate Clinical Professor of Pediatrics, Stanford University School of Medicine; Chief of Pediatrics, Mt. Zion Hospital, San Francisco, Calif.

Rhoda Schneider, B.Sc.

Clinical Laboratories, Medical Centre, Johannesburg, South Africa.

Marvin R. Shetlar, Ph.D.

Associate Professor of Biochemistry, University of Oklahoma School of Medicine; Formerly, Chief of Research Laboratories, Veterans Administration Hospital, Oklahoma City, Okla.

Maurice Sokolow, M.D.

Associate Professor of Medicine and Chief of Cardiovascular Division of the Department of Medicine, University of California School of Medicine, San Francisco, Calif.

Louis A. Soloff, M.D.

Clinical Professor of Medicine, Temple University School of Medicine and Hospital; Chief of Medicine, Episcopal Hospital, Philadelphia, Pa.

Norman Solomon, B.A.

Senior Medical Student, State University of New York, Upstate Medical Center, Syracuse, N. Y.

HOWARD B. SPRAGUE, M.D.

Physician and Member of the Board of Consultation, Massachusetts General Hospital; Lecturer on Medicine, Harvard Medical School, Boston, Mass.

BRIAN J. SPROULE, M.D., M.S.

Clinical Research Fellow, Cardiopulmonary Laboratory of the Department of Internal Medicine, University of Texas Southwestern Medical School, Dallas, Tex.

WENDELL STAINSBY, SC.D.

Senior Assistant Surgeon, Laboratory of Cardiovascular Physiology, National Heart Institute; Presently, University of Florida, Gainesville, Fla.

RICHARD W. STONE, M.D.

Clinical Assistant Professor of Medicine, State University of New York, College of Medicine, Downstate Medical Center, Brooklyn, New York; Assistant Visiting Physician, Second Pulmonary Disease Division, Kings County Hospital, Brooklyn, N. Y.

PHILIP G. STRAUSS, M.D.

Clinical Instructor in Medicine, University of California Hospital; Formerly, Fellow in Cardiac Radiology, Stanford University Hospitals, San Francisco, Calif.

W. W. STREET, M.D.

Clinical Professor of Medicine, State University of New York, Upstate Medical Center, Syracuse, N. Y.

A. H. TOOMAJIAN, B.A.

Senior Medical Student, State University of New York, Upstate Medical Center, Syracuse, N. Y.

JAMES V. WARREN, M.D.

Professor of Medicine, Department of Medicine, Duke University, Durham, N. C.

ARNOLD M. WEISSLER, M.D.

American Heart Association Research Fellow; Instructor in Medicine, Department of Medicine, Duke University, Durham, N. C.

STEWART G. WOLF, JR.

Professor and Head of Department of Medicine; Consultant Professor of Neurology and Psychiatry, University of Oklahoma Medical Center; Head of the Psychosomatic and Neuromuscular Section, Oklahoma Medical Research Foundation, Oklahoma City, Okla.

NANCY WU, M.D.

Formerly, Instructor, Internal Medicine, University of Texas Southwestern Medical School, Dallas, Tex.; Presently, Anesthesiologist, Massachusetts Memorial Hospitals, Boston, Mass.

CIRCULATION

Official Journal of the American Heart Association

VOLUME XVII
January—June 1958

GRUNE & STRATTON, INC.
NEW YORK AND LONDON

CIRCULATION

OFFICIAL JOURNAL OF THE AMERICAN HEART ASSOCIATION

EDITOR-IN-CHIEF

HERRMAN L. BLUMGART, *Boston, Mass.*

EDITH E. PARRIS, *Assistant Editor*

EDITORIAL BOARD

E. COWLES ANDRUS, *Baltimore, Md.*
BENJAMIN M. BAKER, *Baltimore, Md.*
JANET S. BALDWIN, *New York, N. Y.*
SAMUEL BELLET, *Philadelphia, Pa.*
RICHARD J. BING, *St. Louis, Mo.*
STANLEY E. BRADLEY, *New York, N. Y.*
HOWARD B. BURCHELL, *Rochester, Minn.*
A. C. CORCORAN, *Cleveland, Ohio*
ANDRÉ COURNAND, *New York, N. Y.*
JEFFERSON M. CRISMON, *Stanford, Calif.*
CLARENCE DE LA CHAPELLE, *New York, N. Y.*
ALBERT DORFMAN, *Chicago, Ill.*
CHARLES T. DOTTER, *Portland, Ore.*
JESSE E. EDWARDS, *Rochester, Minn.*
J. RUSSELL ELKINTON, *Philadelphia, Pa.*
A. CARLTON ERNSTENE, *Cleveland, Ohio*
A. STONE FREEDBERG, *Boston, Mass.*
CHARLES K. FRIEDBERG, *New York, N. Y.*
HARRY GOLDBLATT, *Cleveland, Ohio*
ROBERT E. GROSS, *Boston, Mass.*
HANS H. HECHT, *Salt Lake City, Utah*
LOUIS N. KATZ, *Chicago, Ill.*
AARON KELLNER, *New York, N. Y.*
CHARLES E. KOSSMANN, *New York, N. Y.*
WALTER F. KVALE, *Rochester, Minn.*
JERE W. LORD, *New York, N. Y.*
H. M. MARVIN, *New Haven, Conn.*
THOMAS M. MCMILLAN, *Philadelphia, Pa.*
DICKINSON W. RICHARDS, *New York, N. Y.*
FREDRICK J. STARE, *Boston, Mass.*
ISAAC STARR, *Philadelphia, Pa.*
HELEN B. TAUSSIG, *Baltimore, Md.*
JAMES WATT, *Bethesda, Md.*
CHARLES C. WOLFERTH, *Philadelphia, Pa.*
EARL H. WOOD, *Rochester, Minn.*
IRVING S. WRIGHT, *New York, N. Y.*

ASSOCIATE EDITORS

EDGAR V. ALLEN, *Rochester, Minn.*
STANFORD WESSLER, *Boston, Mass.*
PAUL M. ZOLL, *Boston, Mass.*

PUBLICATIONS COMMITTEE AMERICAN HEART ASSOCIATION

J. SCOTT BUTTERWORTH, *Chairman*, *New York, N. Y.*

STANLEY E. BRADLEY, *New York, N. Y.*
LUDWIG W. EICHNA, *New York, N. Y.*
IRVING B. HEXTER, *Cleveland, Ohio*
CLIFTON D. HOWE, *Houston, Texas*
JAMES WATT, *Bethesda, Md.*

GEORGE E. WAKERLIN, *Medical Director, American Heart Association, New York, N. Y.*

HERRMAN L. BLUMGART, *Boston, Mass.*
HOWARD P. LEWIS, *Portland, Ore.*
CARL F. SCHMIDT, *Philadelphia, Pa.*

Interlingua Summaries by Science Service, Division de Interlingua, New York, N.Y., ALEXANDER GODE, Chief.

VOLUME XVII

January-June, 1958

CIRCULATION

Official Journal of the American Heart Association

No. 1

EDITORIAL

EMOTIONAL STRESS AND THE ETIOLOGY OF CORONARY ARTERY DISEASE. *Howard B. Sprague* 1

SYMPATHECTOMY FOR RAYNAUD'S PHENOMENON: FOLLOW-UP STUDY OF 70 WOMEN WITH SECONDARY RAYNAUD'S PHENOMENON. *Ray W. Gifford, Jr., Edgar A. Hines and Winchell McK. Craig* 5

PREDICTIVE VALUE OF LIPOPROTEIN AND CHOLESTEROL DETERMINATIONS IN DIABETIC PATIENTS WHO DEVELOPED CARDIOVASCULAR COMPLICATIONS. *Alexander D. Lowy, Jr. and Joseph H. Barach* 14

NITROGLYCERIN AND OTHER NITRITES IN THE TREATMENT OF ANGINA PECTORIS: COMPARISON OF SIX PREPARATIONS AND FOUR ROUTES OF ADMINISTRATION. *Joseph E. F. Riseman, George E. Altman and Sidney Koretsky* 22

ENDOCARDIAL FIBROELASTOSIS: ANGIOCARDIOGRAPHIC STUDIES. *Leonard M. Linde, Forrest H. Adams and Bernard J. O'Loughlin* 40

COMPARISON OF FOUR ORTHOGONAL SYSTEMS OF VECTORCARDIOGRAPHY. *Paul H. Langner, Jr., Robert H. Okada, Samuel R. Moore and Harry L. Fies* 46

PULMONARY ARTERY STENOSIS. *Margaret B. Vermillion, Leonard Leight and Lawrence A. Davis* 55

MASSIVE OCCLUSION OF THE MAIN PULMONARY ARTERY AND PRIMARY BRANCHES: CASE REPORT. *Jorma M. Leinassar and Nelson R. Niles* 60

THE EMPHYSEMA RESPONSE TO FORCED STRAINING (VALSALVA'S MANEUVER). *Harold Mills and Albert A. Kattus, Jr.* 65

CONGENITAL MALFORMATIONS OF THE HEART ASSOCIATED WITH SPLENIC AGENESIS: WITH A REPORT OF FIVE CASES. *Enid F. Gilbert, Kinsuke Nishimura and Bernice G. Wedum* 72

THE BALLISTOCARDIOGRAM IN OVERWEIGHT YOUNG ADULTS. *Samuel Stern* .. 87

THE ATRIAL CORONARY ARTERIES IN MAN. *Thomas N. James and George E. Burch* 90

INFLUENCE OF SOME FACTORS ON DEVELOPMENT OF EXPERIMENTAL CHOLESTEROL ATHEROSCLEROSIS. *A. L. Myasnikov* 99

PANEL DISCUSSION

REHABILITATION OF THE CARDIAC PATIENT. *Louis N. Katz, Robert A. Bruce, Norman Plummer and Herman K. Hellerstein* 114

CLINICAL PROGRESS

ECHINOCOCCUS DISEASE OF THE HEART. *Jorge Dighiero, Eduardo Joaquín Canabal, Cesar C. Aguirre, Jacobo Hazan and José O. Horjales* 127

Book Reviews 133
Abstracts 141
American Heart Association 155
Contributors to this Issue 159

No. 2

Editorial
Clinical Aspects of Some Diseases of the Small Arteries and Arterioles. *Edgar A. Hines, Jr.* 161
Pulmonary Heart Disease: With Emphasis on Electrocardiographic Diagnosis. *Robert N. Armen, Milton Kanton and Nelson J. Weiser* 164
Serum Cholesterol in Pentolinium-Treated Arterial Hypertension. *Harold H. Orvis, Irene G. Tamagna and John M. Evans* 176
Pulmonic Stenosis with Intact Ventricular Septum: Treatment Utilizing Extracorporeal Circulation. *Dwight C. McGoon and John W. Kirklin* 180
Intravenous Protein-Free Pyrogen: A Powerful Fibrinolytic Agent in Man. *Kurt N. von Kaulla* 187
Inaccuracy of Wedge Pressure as an Index of Pulmonary Capillary Pressure. *Jerome P. Murphy* 199
Severe Hemoptysis During Pregnancy Treated by Mitral Commissurotomy. *William F. M. Fulton and George Smith* 204
Interrelationships of Drugs Influencing Arterial Pressure in Man. *Walter Redisch, Francisco F. Tangco, Arthur J. Lewis, Maria Aurora Antonio, Kurt DeCrinis and J. Murray Steele* 208
Left Atrial Electrokymography in Mitral Insufficiency in Man: A Correlative Study by Angiocardiography and Left Heart Catheterization. *Richard D. Judge, Melvin M. Figley and Herbert E. Sloan* 213
Ventricular Precontracting Area in the Wolff-Parkinson-White Syndrome: Demonstration in Man. *Giulio Bandiera and Pier Fausto Antognetti* 225
Patent Ductus Arteriosus in Association with Pulmonic Stenosis: A Report of Six Cases with Additional Noncardiac Congenital Anomalies. *Douglas C. Heiner and Alexander S. Nadas* 232
Clinicopathologic Correlations of Renal Biopsies in Hypertension with Pyelonephritis. *Joseph C. Merriam, Sheldon C. Sommers and Reginald H. Smithwick* 243
Corrected Transposition of the Great Vessels, Atrioventricular Heart Block and Ventricular Septal Defect: A Clinical Triad. *Weldon J. Walker, Denton A. Cooley, Dan G. McNamara and Robert H. Moser* 249
Reliability of Electrocardiographic Diagnosis of Left Ventricular Hypertrophy. *Arthur Selzer, Carl L. Ebnother, Peter Packard, Arthur O. Stone and John E. Quinn* 255
Dextrocardia with Pulmonary Stenosis and Functionally Single Right Ventricle. *Joseph Fisher and Soon Kyu Suh* 266
Anatomic Studies of the Cardiac Conduction System in Congenital Malformations of the Heart. *Keith Reemtsma and W. M. Copenhaver* 271

Influence of an Oscillating Bed on Cutaneous Temperature and Oxygen Tension of Ischemic Toes. *Carlos Forno, Hugh Montgomery and Orville Horwitz* 277
The Nitrous Oxide Test: An Improved Method for the Detection of Left-to-Right Shunts. *Andrew G. Morrow, Richard J. Sanders and Eugene Braunwald* 284
Clinical Progress
Anesthesia in Patients with Heart Disease. *Leroy D. Vandam and Thomas K. Burnap* 292
Abstracts 299
American Heart Association 315
Contributors to this Issue 318

No. 3

Editorial
Epidemiology and Coronary Heart Disease. *J. N. Morris* 321
Intravenous Drug Therapy of Stokes-Adams Disease: Effects of Sympathomimetic Amines on Ventricular Rhythmicity and Atrioventricular Conduction. *Paul M. Zoll, Arthur J. Linenthal, William Gibson, Milton H. Paul and Leona R. Norman* 325
Infradiaphragmatic Total Anomalous Pulmonary Venous Connection. *Arnold L. Johnson, F. W. Wigglesworth, J. S. Dunbar, Sarjit Siddoo and Maria Grajo* 340
Long-Term Treatment of Angina Pectoris with Dicumarol. *Zeth Gabrielsen and Jon R. Myhre* 348
Bronchoscopic Method for Measuring Left Atrial Pressure: An Aid to Diagnosis in Mitral Disease. *A. J. Gunning and R. J. Linden* 354
Coexistence of Patent Ductus Arteriosus and Congenital Aortic Valvular Disease. *Herbert Mark, Belle Jacobson and Dennison Young* 359
Biosynthesis of Epinephrine and Norepinephrine by Sympathetic Nerves and Ganglia. *McC. Goodall and Norman Kirshner* 366
Coronary Arteriovenous Fistula. *Israel Steinberg, Janet S. Baldwin and Charles T. Dotter* 372
Blood Supply of the Human Interventricular Septum. *Thomas N. James and George E. Burch* 391
The Concept of "Masquerading" Bundle-Branch Block: An Electrocardiographic-Pathologic Correlation. *Paul N. Unger, Milton E. Lesser, Victor H. Kugel and Maurice Lev* 397
Physical Factors in the Progression of Stenotic Vascular Lesions. *Simon Rodbard* 410
Bronchial Obstruction Due to Pulmonary Artery Anomalies: I. Vascular Sling. *Stephen Contro, Robert A. Miller, Harvey White and Willis J. Potts* 418
Bronchial Obstruction Due to Pulmonary Artery Anomalies: II. Pulmonary Artery Aneurysm. *Stephen Contro, Robert A. Miller, Harvey White and Willis J. Potts* 424
Special Article
William Harvey Speaks. *Edgar V. Allen* 428

CLINICAL CONFERENCE

COARCTATION OF AORTA COMPLICATED BY BACTERIAL ENDOCARDITIS AND AN ANEURYSM OF THE SINUS OF VALSALVA. *Frank Glenn, Harold J. Stewart, Mary A. Engle, Daniel S. Lukas, Joseph Artusio, Israel S. Steinberg and George R. Holswade* 432

CLINICAL PROGRESS

EFFECT OF SMOKING ON THE CARDIOVASCULAR SYSTEM OF MAN. *Grace M. Roth and Richard M. Shick* 443

ABSTRACTS 460

AMERICAN HEART ASSOCIATION 476

CONTRIBUTORS TO THIS ISSUE 479

No. 4

PART ONE

EDITORIAL

INTERPRETATION OF CARDIOVASCULAR PRESSURE PULSES. *David F. Opdyke* 481

PRESIDENTIAL ADDRESS: OUR SECOND DECADE. *Robert W. Wilkins* 484

THE GEORGE E. BROWN MEMORIAL LECTURE: CURRENT STATUS OF THE PROBLEM OF THROMBOSIS. *Nelson W. Barker* 487

TREATMENT OF HYPERCHOLESTEROLEMIA WITH NICOTINIC ACID. *Richard W. P. Achor, Kenneth G. Berge, Nelson W. Barker and Bernard F. McKenzie* 497

A METHOD FOR THE DETECTION AND ESTIMATION OF AORTIC REGURGITANT FLOW IN MAN. *Eugene Braunwald and Andrew G. Morrow* 505

STUDIES IN PERIPHERAL ARTERIAL OCCLUSIVE DISEASE: III. ACUTE ARTERIAL OCCLUSION. *Stanford Wessler, Sheldon G. Sheps, Marvin Gilbert and Mindel C. Sheps* 512

CARDIOVASCULAR HEMODYNAMIC FUNCTIONS IN COMPLETE HEART BLOCK AND THE EFFECT OF ISOPROPYLNOREPINEPHRINE. *Maria F. Stack, Bertha Rader, Bruce J. Sobol, Saul J. Farber and Ludwig W. Eichna* 526

HEREDITY, ENVIRONMENT, AND SERUM CHOLESTEROL: A STUDY OF 201 HEALTHY FAMILIES. *Louis E. Schaefer, David Adlersberg and Arthur G. Steinberg* 537

VALUE OF AN ELECTRODE CATHETER IN DIAGNOSIS OF EBSTEIN'S DISEASE. *Bernard J. B. Yim and Paul N. Yu* 543

POSTPERICARDIOTOMY SYNDROME FOLLOWING SURGERY FOR NONRHEUMATIC HEART DISEASE. *Tomiko Ito, Mary Allen Engle and Henry P. Goldberg* 549

UNILATERAL PULMONARY ARTERY ABSENCE OR HYPOPLASIA: RADIOGRAPHIC AND CARDIOPULMONARY STUDIES IN FIVE PATIENTS. *John C. Elder, Bernard L. Brofman, Paul M. Kohn and Bernard L. Charms* 557

ANGIOCARDIOGRAPHIC AND PHYSIOLOGIC CORRELATIONS IN MITRAL STENOSIS. *Daniel S. Lukas, Peter R. Mahrer and Israel Steinberg* 567

ELECTROLYTE AND WATER EXCRETION IN ARTERIAL HYPERTENSION: II. STUDIES IN SUBJECTS WITH ESSENTIAL HYPERTENSION AFTER ANTIHYPERTENSIVE DRUG TREATMENT. *William Hollander and Walter E. Judson* .. 576

MUSCULAR DYSTROPHY: CATHETERIZATION STUDIES INDICATING LATENT CONGESTIVE HEART FAILURE. *S. Gailani, T. S. Danowski and D. S. Fisher* 583

Studies Made by Simulating Systole at Necropsy: XI. On the Higher Dynamic Functions of the Heart and Their Reflections in the Pulse Wave. *Isaac Starr* 589
Clinical Progress
Systolic Murmurs. *Aubrey Leatham* 601
Abstracts 612
American Heart Association 629
Contributors to this Issue 639

PART TWO

Basic Mechanisms of Arterial Hypertension: Foreword 641
Experimental Renal Hypertension: Mechanism of Production and Maintenance. *Harry Goldblatt* 642
Studies on Renin Antibodies. *Oscar M. Helmer* 648
Antibodies to Renin as Proof of the Pathogenesis of Sustained Renal Hypertension. *George E. Wakerlin* 653
Renal Pressor System in Hypertension: Evidence for Circulating Hypertensin in Chronic Renal Hypertension—Nature and Activity of Purified Hypertensin. *Leonard T. Skeggs and Joseph R. Kahn* .. 658
Synthesis and Properties of Angiotonin. *F. Merlin Bumpus, Hans Schwarz and Irvine H. Page* 664
Pressor Polypeptides Formed in Vivo and in Vitro as Mediators of Renal Hypertension. *E. Braun-Menéndez and A. C. Paladini* 668
Studies on the Renal Humoral Mechanism of Chronic Experimental Hypertension. *Alberto C. Taquini, Pedro Blaquier and Alberto C. Taquini, Jr.* 672
Discussion of Reports on Renal Factors in Hypertension 676
Conference on the Role of the Renal Pressor System in Maintenance of Experimental Renal Hypertension. *Led by Harry Goldblatt* 683
Introductory Remarks Concerning the Urologic Aspects of Hypertension. *R. M. Nesbit* 693
Evidence for Renotrophin as a Causal Factor in Renal Hypertension. *E. Braun-Menéndez* 696
Reduction of Experimental Renal Hypertension by Kidney Perfusion. *W. J. Kolff* 702
Evidence for Humoral Factors in Renoprival Hypertension. *Paul A. Rondell, Ruth B. McVaugh and David F. Bohr* 708
Discussion of Reports on Renoprival Hypertension 714
Conference on Mechanism of Protective Action of Kidney and Relation of Renoprival to Chronic Renal Hypertension. *Led by E. Braun-Menéndez* 719
Panel Discussion on Genetic and Environmental Factors in Human Hypertension. *K. G. Kohlstaedt, M. Moser, T. Francis, Jr., J. Neel and F. Moore* 728
Adrenal Factors in Hypertension. *Jerome W. Conn* 743
Effect of Electrolytes on Arterial Muscle Contraction. *David F. Bohr, Donald C. Brodie and Donald H. Cheu* 746

Effect of an Intravenous Sodium Chloride Load on Renal Hemodynamics and Electrolyte Excretion in Essential Hypertension. *Paul T. Cottier, John M. Weller and Sibley W. Hoobler* 750
Serum Magnesium and Plasma Sodium Levels in Essential Vascular Hypertension. *Donald G. Albert, Yoshikazu Morita and Lloyd T. Iseri* 761
Contribution of the Adrenal Cortex to Renal and Renoprival Hypertension. *Harriet P. Dustan and Georges M. C. Masson* 765
Discussion of Reports on Electrolyte and Adrenal Factors in Hypertension. 768
Conference on Electrolyte and Adrenal Factors in Human and Experimental Renal Hypertension. *Led by David F. Bohr* 771
Introductory Remarks Concerning Neural Factors in Essential Hypertension. *Edgar A. Kahn* 782
Baroceptor and Sympathetic Activity in Experimental Renal Hypertension in the Dog. *Paul Kezdi and James R. Wennemark* 785
Carotid Sinus Participation in Experimental Renal Hypertension. *J. W. McCubbin* 791
Effect of the Autonomic Nervous System on Arteriolar Tone in the Experimental Animal. *Lloyd Beck* 798
Vascular Reactivity in Experimental Hypertension Measured after Hexamethonium. *James Conway* 807
Discussion of Reports on Neural Factors in Hypertension 811
Conference on Neural Control of the Circulation in Hypertension. *Led by Sibley W. Hoobler* 815
An Interpretive Review of the Conference Proceedings. *Sibley W. Hoobler* 825
Index to Contributors and Bibliography 833
Contributors to this Issue 837

No. 5

Editorial
How to Write an Abstract. *Robert W. Wilkins* 841
The Lewis A. Conner Memorial Lecture: Rheumatic Heart Disease—A Challenge. *Charles A. Rammelkamp* 842
Changes in the Serum Cholesterol and Blood Clotting Time in Men Subjected to Cyclic Variation of Occupational Stress. *Meyer Friedman, Ray H. Rosenman and Vernice Carroll* 852
Regression After Open Valvotomy of Infundibular Stenosis Accompanying Severe Valvular Pulmonic Stenosis. *Mary Allen Engle, George R. Holswade, Henry P. Goldberg, Daniel S. Lukas and Frank Glenn* 862
Electrocardiograms of Ninety Patients with Acrosclerosis and Progressive Diffuse Sclerosis (Scleroderma). *John H. Windesheim and Thomas W. Parkin* 874
A Method for the Electrocardiographic Recognition of Atrial Enlargement. *Radi Macruz, Joseph K. Perloff and Robert R. Case* 882
Response of Serum Lipids and Lipoproteins of Man to Beta-Sitosterol and Safflower Oil: A Long Term Study. *John W. Farquhar and Maurice Sokolow* 890

Radioiodine Treatment of Paroxysmal Supraventricular Tachycardia in the Euthyroid Patient. *Eliot Corday, Herbert Gold, and Henry L. Jaffe* 900
Intramural Hemorrhage in Coronary Atherosclerosis. *Thomas M. Blake and Philip K. Springer* 907
Total Electrical Alternation in Pericardial Disease. *David Littmann and David H. Spodick* 912
Effectiveness of an Oral, Nonmercurial Diuretic: Clinical Trial with Thirty-Five Patients. *Benjamin Wainfeld, Jacob J. Yarvis and I. Richard Schwartz* 918
Reliability of Subjective Circulation Time Determinations: A Comparison Between Objective and Subjective Methods. *Murray M. Mahl and Kurt Lange* 922
Alimentary Lipemia and the Coagulability of Blood: Analysis by Thrombeplastography and Silicone Clotting Time. *Thomas W. Sheehy and James W. Eichelberger* 927
Further Experiences with Blood Coagulation after Fat Meals and Carbohydrate Meals. *Jaime Borrero, Erwin Sheppard and Irving S. Wright* 936
Primary Aortic Thrombosis. *H. Gaylis* 941
Clinical Conference
Long-Term Management of Patients with Coronary Artery Disease. *Laurence B. Ellis, Hermann L. Blumgart, Dwight E. Harken, Herbert S. Sise and Fredrick J. Stare* 945
Clinical Progress
Penetrating Wounds of the Heart and Aorta: Part I. Penetrating Wounds of the Heart. *Loren F. Parmley, Thomas W. Mattingly and William C. Manion* 953
Abstracts 974
American Heart Association 995
Contributors to this Issue 999

No. 6

Editorial
Anomalous Coronary Arteries with Special Reference to Arteriovenous-like Communications. *Jesse E. Edwards* 1001
Observations on the Mechanism of Atrial Gallop Rhythm. *James J. Leonard, Arnold M. Weissler and James V. Warren* 1007
Osmotic Diuretic Treatment of Refractory Edema. *Lionel M. Bernstein, Bernard Blumberg and Murray C. Arkin* 1013
Serum Lipids in South African Bantu and White Subjects. *B. M. Bloomberg, F. Lazarus, Irene Mrost and Rhoda Schneider* 1021
Venous-Arterial Admixture in the Lungs in Primary and Secondary Polycythemia. *James P. Lillehei, Robert L. Johnson, Jr., Nancy Wu, E. Richard Halden and Brian J. Sproule* 1029
Serum Lipid and Estrogenic Effects of Manvene, A New Estrogen Analog: Comparison with Premarin in Men with Coronary Heart Disease. *William D. Cohen, Norio Higano and Roger W. Robinson* 1035

AN EVALUATION OF BLOOD NITRATE LEVELS. *John W. Berry and Thomas C. Roach* 1041

RADIOLOGIC ASPECTS OF OPERABLE HEART DISEASE: VI. CHANGES FOLLOWING SURGICAL CLOSURE OF PATENT DUCTUS ARTERIOSUS. *Philip Strauss, Herbert L. Abrams and Saul Robinson* 1047

PULMONARY COMPLIANCE IN PATIENTS WITH PERIODIC BREATHING. *Harold A. Lyons, Frank Burno and Richard W. Stone* 1056

ANOMALOUS ORIGIN OF THE LEFT CORONARY ARTERY: THE PHYSIOLOGIC DEFECT AND SUGGESTED SURGICAL TREATMENT. *Robert B. Case, Andrew G. Morrow, Wendell Stainsby and John O. Nestor* 1062

CLINICAL OBSERVATIONS WITH THE FRANK PRECORDIAL LEAD SYSTEM. *J. A. Abildskov, W. W. Street, N. Solomon and A. H. Toomajian* 1069

A COMPARISON OF THE SERUM LIPIDS, LIPOPROTEINS, GLYCOPROTEINS, URINARY 17-KETOSTEROIDS, AND GONADOTROPINS IN EUNUCHS AND CONTROL MALE SUBJECTS. *Robert H. Furman, R. Palmer Howard, M. R. Shetlar, E. Corinne Keaty and Richard Imagawa* 1076

NONPENETRATING TRAUMATIC INJURY OF THE AORTA. *Loren F. Parmley, Thomas W. Mattingly, William C. Manion and Edward J. Jahnke, Jr.* 1086

THE NORMAL ORTHOGONAL ELECTROCARDIOGRAM AND VECTORCARDIOGRAM: WITH A CRITIQUE OF SOME COMMONLY USED ANALYTIC CRITERIA. *Hubert V. Pipberger* 1102

PANEL DISCUSSION

PREVENTION AND MANAGEMENT OF CARDIOVASCULAR EMERGENCIES. *Howard B. Sprague, James Metcalfe, Benjamin M. Gasul, Louis A. Soloff, Maurice Sokolow and Stewart G. Wolf, Jr.* 1112

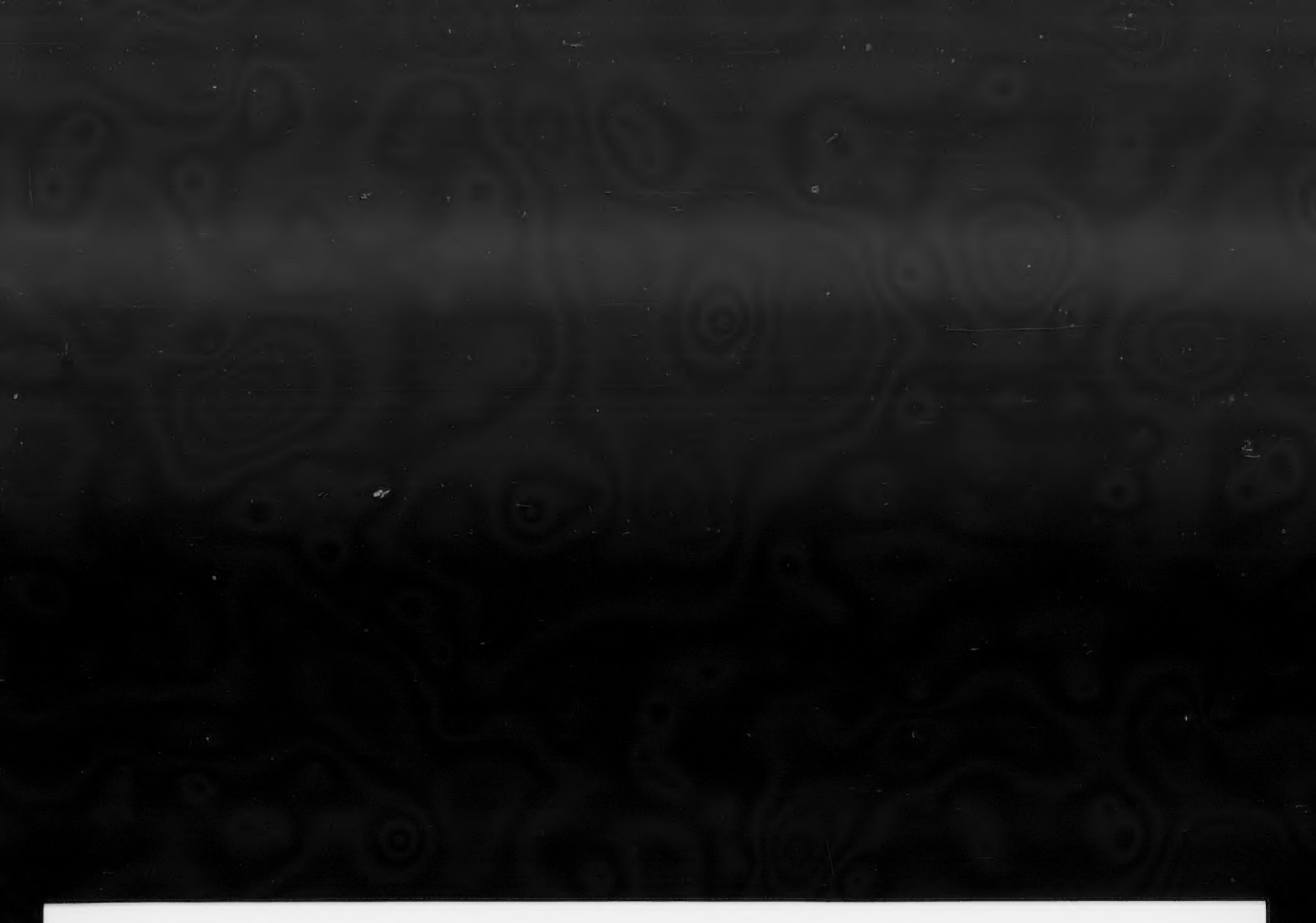
CLINICAL PROGRESS

MANAGEMENT OF SPONTANEOUS INTRACRANIAL SUBARACHNOID HEMORRHAGE. *H. Thomas Ballantine, Jr. and David M. Klein* 1123

ABSTRACTS 1137

AMERICAN HEART ASSOCIATION 1154

CONTRIBUTORS TO THIS ISSUE 1158



INDEX OF AUTHORS

Abildskov, J. A., 1069
Abrams, H. L., 1047
Achor, R. W. P., 497
Adams, F. H., 40
Adlersberg, D., 537
Aguirre, C. V., 127
Albert, D. G., 761
Allen, E. V., 428
Altman, G. E., 22
Antognetti, P. F., 225
Antonio, M. A., 208
Arkin, M. C., 1013
Armen, R. N., 164
Artusio, J., 432

Baldwin, J. S., 372
Ballantine, H. T., Jr., 1123
Bandiera, G., 225
Barach, J. H., 14
Barker, N. W., 487, 497
Beck, L., 798
Berge, K. G., 497
Bernstein, L. M., 1013
Berry, J. W., 1041
Blake, T. M., 907
Blaquier, P., 672
Bloomberg, B. M., 1021
Blumberg, B., 1013
Blumgart, H. L., 945
Bohr, D. F., 708, 746, 771
Borrero, J., 936
Braun-Menéndez, E., 668, 696, 719
Braunwald, E., 284, 505
Brodie, D. C., 746
Brofman, B. L., 557
Bruce, R. A., 114
Bumpus, F. M., 664
Burch, G. E., 90, 391
Burnap, T. K., 292
Burno, F., 1056

Canabal, E. J., 127
Carroll, V., 852
Case, R. B., 882, 1062
Charms, B. L., 557
Cheu, D. H., 746
Cohen, W. D., 1035
Conn, J. W., 743
Contro, S., 418, 424
Conway, J., 807
Cooley, D. A., 249
Copenhaver, W. M., 271
Corday, E., 900
Cottier, P. T., 750
Craig, W. McK., 5

Danowski, T. S., 583
Davis, L. A., 55
DeCrinis, K., 208
Dighiero, J., 127
Dotter, C. T., 372
Dunbar, J. S., 340
Dustan, H. P., 765

Ebnother, C. L., 255
Edwards, J. E., 1001
Eichelberger, J. W., Jr., 927
Eichna, L. W., 526
Elder, J. C., 557
Ellis, L. B., 945
Engle, M. A., 432, 549, 862
Evans, J. M., 176

Farber, S. J., 526
Farquhar, J. W., 890
Fies, H. L., 46
Figley, M. M., 213
Fisher, D. S., 583
Fisher, J., 266
Forno, C., 277
Francis, T., 728
Friedman, M., 852
Fulton, W. F. M., 204
Furman, R. H., 1076

Gabrielsen, Z., 348
Gailani, S., 583
Gasul, B. M., 1112
Gaylis, H., 941
Gibson, W., 325
Gifford, R. W., Jr., 5
Gilbert, E. F., 72
Gilbert, M., 512
Glenn, F., 432, 862
Gold, H., 900
Goldberg, H. P., 549, 862
Goldblatt, H., 642, 683
Goodall, McC., 366
Grajo, M., 340
Gunning, A. J., 354

Halden, E. R., 1029
Harken, D. E., 945
Hazan, J., 127
Heiner, D. C., 232
Hellerstein, H. K., 114
Helmer, O. M., 648
Higano, N., 1035
Hines, E. A., Jr., 5, 161
Hollander, W., 576
Holswade, G. R., 432, 862
Hoobler, S. W., 750, 815, 825
Horjales, J. O., 127
Horwitz, O., 277
Howard, R. P., 1076

Imagawa, R., 1076
Iseri, L. T., 761
Ito, T., 549

Jacobson, B., 359
Jaffe, H. L., 900
Jahnke, E. J., Jr., 1086
James, T. N., 90, 391
Johnson, A. L., 340
Johnson, R. L., Jr., 1029
Judge, R. D., 213
Judson, W. E., 576

Kahlstaedt, K. G., 728
Kahn, E. A., 782
Kahn, J, R., 658
Kanton, M., 164
Kattus, A. A., Jr., 65
Katz, L. N., 114
Keaty, E. C., 1076
Kezdi, P., 785
Kirklin, J. W., 180
Kirshner, N., 366
Klein, D. M., 1123
Kohn, P. M., 557
Kolff, W. J., 702
Koretsky, S., 22
Kugel, V. H., 397

Lange, K., 922
Langner, P. H., Jr., 46
Lazarus, F., 1021
Leatham, A., 601
Leight, L., 55
Leinassar, J. M., 60
Leonard, J. J., 1007
Lesser, M. E., 397
Lev, M., 397
Lewis, A. J., 208
Lillehei, J. P., 1029
Linde, L. M., 40
Linden, R. J., 354
Linenthal, A. J., 325
Littmann, D., 912
Lowy, A. D., Jr., 14
Lukas, D. S., 432, 567, 862
Lyons, H. A., 1056

Maeruz, R., 882
Mahl, M. M., 922
Mahrer, P. R., 567
Manion, W. C., 953, 1086
Mark, H., 359
Masson, G. M. C., 765
Mattingly, T. W., 953, 1086
McCubbin, J. W., 791
McGoon, D. C., 180
McKenzie, B. F., 497
McNamara, D. G., 249
McVaugh, R. B., 708
Merriam, J. C., 243
Metcalfe, J., 1112
Miller, R. A., 418, 424
Mills, H., 65
Montgomery, H., 277
Moore, F., 728
Moore, S. R., 46
Morita, Y., 761
Morris, J. N., 321
Morrow, A. G., 284, 505, 1062
Moser, M., 728
Moser, R. H., 249
Mrost, I., 1021
Murphy, J. P., 199
Myasnikov, A. L., 99
Myhre, J. R., 348

Nadas, A. S., 232
Neel, J., 728
Nesbit, R. M., 693
Nestor, J. O., 1062
Niles, N. R., 60
Nishimura, K., 72
Norman, L. R., 325

Okada, R. H., 46
O'Loughlin, B. J., 40
Opdyke, D. F., 481
Orvis, H. H., 176

T. P. T Contents moved to front of Vol.

Packard, P., 255
Page, I. H., 664
Paladini, A. C., 668
Parkin, T. W., 874
Parmley, L. F., 953, 1086
Paul, M. H., 325
Perloff, J. K., 882
Pipberger, H. V., 1102
Plummer, N., 114
Potts, W. J., 418, 424

Quinn, J. E., 255

Rader, B., 526
Rammelkamp, C. A., 842
Redisch, W., 208
Reemtsma, K., 271
Riseman, J. E. F., 22
Roach, T. C., 1041
Robinson, R. W., 1035
Robinson, S., 1047
Rodbard, S., 410
Rondell, P. A., 708
Rc- ıan, R. H., 852
R M., 443

Sanders, R. J., 284
Schaefer, L. E., 537
Schneider, R., 1021
Schwartz, I. R., 918
Schwarz, H., 664
Selzer, A., 255
Sheehey, T. W., 927
Sheppard, E., 936
Sheps, M. C., 512
Sheps, S. G., 512
Shetlar, M. R., 1076
Shick, R. M., 443
Siddoc, S., 340
Sise, H. S., 945
Skeggs, L. T., 658
Sloan, H. E., 213
Smith, G., 204
Smithwick, R. H., 243
Sobol, B. J., 526
Sokolow, M., 890, 1112
Soloff, L. A., 1112
Solomon, N., 1069
Sommers, S. C., 243
Spodick, D. H., 912
Sprague, H. B., 1, 1112
Springer, P. K., 907
Sproule, B. J., 1029
Stack, M. F., 526
Stainsby, W., 1062
Stare, F. J., 945
Starr, I., 589
Steele, J. M., 208
Steinberg, A. G., 537
Steinberg, I. S., 372, 432, 567
Stern, S., 87
Stewart, H. J., 432
Stone, A. O., 255
Stone, R. W., 1056
Strauss, P., 1047
Street, W. W., 1069
Suh, S. K., 266

Tamagna, I. G., 176
Tangeo, F. F., 208
Taquini, A. C., 672
Taquini, A. C., Jr., 672
Toomajian, A. H., 1069

Unger, P. N., 397

Vandam, L. D., 292
Vermillion, M. B., 55
von Kaulla, K. N., 187

Wainfeld, B., 918
Wakerlin, G. E., 653
Walker, W. J., 249
Warren, J. V., 1007
Wedum, B. G., 72
Weiser, N. J., 164
Weissler, A. M., 1007
Weller, J. M., 750
Wennemark, J. R., 785
Wessler, S., 512
White, H., 418, 424
Wiglesworth, F. W., 340
Wilkins, R. W., 484, 841
Windesheim, J. H., 874
Wolf, S. G., Jr., 1112
Wright, I. S., 936
Wu, N., 1029

Yarvis, J. J., 918
Yim, B. J. B., 543
Young, D., 359
Yu, P. N., 543

Zoll, P. M., 325

INDEX OF SUBJECTS

Page numbers in italics indicate abstracts

Abdomen, roentgenology of arteries of, *986*
Abdominal aortography, complications of, *988*
Abscess, cerebral, with congenital defects, *299*
Abstracts, how to write, 941
Acceleration studies, 589-599
Acetazoleamide, in respiratory acidosis, *981*
Acetylcholine
atrial fibrillation from, in hypopotassemia, *472*
effects on pulmonary circulation, *472*
heart block from, ouabain in, *153*
Acetyldigitoxin
effects of, *618*, *619*
in heart failure, *462*, *978*
Acrocyanosis, 162
Acrosclerosis, electrocardiography in, 874-880
Adams-Stokes disease, intravenous drug therapy in, 325-338
Adenosine, heart block from, ouabain in, *153*
Adenylic acid infusion, blood flow in, *154*
Adrenal factors in hypertension, 743-744, 765-767, 768-770, 771-781
Adrenalectomy, total, in malignant hypertension, *469*
Aldosterone
activity in disorders, *151*
excretion in sodium and potassium depletion, *983*
and hypertension, *470*
Aldosteronism, electrocardiography in, *1145*
Alimentary lipemia, coagulation in, 927-934, *974*
Allen address, 428-431
Alveolar-capillary block syndrome, *314*
Amblyopia, toxic, from quinidine, *618*
American Heart Association
abstracts due
for Arteriosclerosis Society, 631, 996
for Cardiology Congress, 156
for Scientific Sessions, 155, 476, 629, 995
annual report for 1957, 630
Anticoagulants Symposium, 157
applications for research support, 1154
Arteriosclerosis Society Meetings, 155
attendance at Scientific Sessions, 155
award recipients, 632-638
Blakeslee awards, entries for, 316
Blood Pressure Council officers, 157
booklets for patients on sodium restricted diets, 477
calculus course in Maine, 998
diet leaflet, 997
"Doctors, Heart Associations and United Funds," 476
exhibit applications due, 476
Georgia cardiovascular training program, 477, 631
grants for 1958, 629
to attend Cardiology Congress, 157
Gundersen address, 156
Hawaii Scientific Sessions, 630, 996, 1156
Heart Bulletin, 1156
heart film available, 316
Heart Fund Drive in 1958, 155
Heart Month message from Paul Dudley White, 315
Hypertension Proceedings available, 997, 1156
independent fund policy, 156
meetings calendars, 158, 317, 478, 631, 998, 1157
National Health Forum, 157
Nevada Heart Association, 997
new Cardiology Foundation, 477
new Cardiovascular Research Institute, 996
plans for Scientific Sessions, 315
pulmonary function course, 477
registration for Scientific Sessions, 1154
rheumatic fever
book on, 316
program meeting, 316
proceedings available, 1156
schedule for Scientific Sessions, 995, 1155
steroid biochemistry training program, 631
"Strokes" film, 157
subscription renewals, 157, 316
TV series on research careers, 478, 631, 997
Wakerlin appointment, 630
World Congress of Cardiology, 478, 630
symposia subjects, 997, 1156
travel to, 315
"You and Your Heart" book revised, 316
Amino acid analysis of hypertensin, 662
Aminoaciduria, renal, *623*
Aminophylline, effects on pulmonary circulation, *472*
Amobarbital sodium, effects on cholesterol atherosclerosis, 104
Amputation, transmetatarsal, in diabetes, *990*
Anastomoses
in coronary arteries, coronography of, *978*
interarterial, 518
portacaval, *310*
Anatomic studies of cardiac conduction system, 271-275
Anesthesia in heart disease, 292-298
Anesthetics, and blood pressure responses to epinephrine, *153*
Aneurysm
abdominal aortic
with horseshoe kidney, *308*
leaking, *308*
aortic
post-traumatic, 967, 1086-1100
in pregnancy, *312*
aortic sinus, unperforated, roentgen signs of, *625*
cerebral, in pregnancy, *311*
chronic dissecting, *310*
formation in penetrating heart wounds, 963
intracranial, 1128
ruptured, cause of death in, *308*
popliteal, *311*
pulmonary artery, *305*, 424-427
of sinus of Valsalva, with coaretation of arota and bacterial endocarditis, 432-442
ventricular resection for, *144*
Angina pectoris
anticoagulants in, *463*
EDTA in, *301*
long-term treatment with Dicumarol, 348-352
in mitral disease, *994*
nitrites in, 22-37
radioiodine therapy, 949
surgery in, 950
Angiocardiography
in aortic insufficiency, *987*
bronchial arteries in, 563
in fibroelastosis, endocardial, 40-45
in intracranial hemorrhage, subarachnoid, spontaneous, 1132
in left-to-right shunt through high ventricular septal defect, *308*
in mitral disease, 213-223, *307*, 567-574, *987*
in patent ductus arteriosus, *624*
in pericarditis, constrictive, *306*, *307*
in pulmonary artery absence, unilateral, 557
in thoracic aorta visualization, *307*

Angioma, cerebral, 1127
Angiotonin, 658-663, 664-667, 668
Anoxia, effects on cholesterol atherosclerosis, 107-110
Ansolysen. *See* Pentolinium
Anticoagulants. *See* Coagulation
Antihemophilic factor, storage of, *612*
Antirenin, 646, 648-657
Anxiety, electrocardiogram in, 1122
Aorta
abdominal
aneurysm
with horseshoe kidney, *308*
leaking, *308*
blockage of, arterial dilution curve with, *475*
complications of aortography, *988*
aneurysm
posttraumatic, 967, 1086-1100
in pregnancy, *312*
ascending, calcification of, *624*
coaretation
with bacterial endocarditis and aneurysm of sinus of Valsalva, 432-442
complicated, *462*
resection in, paradoxical hypertension after, *616*
reverse syndrome, *299*
splanchnic circulation in, *1142*
electrolytes in hypertension, *1148*
surgery of, direct vision, *988*
after surgery for patent ductus arteriosus, 1050
thoracic, angiocardiography in visualization of, *307*
thrombosis
hypertension from, *1149*
primary, 941-944
trauma
nonpenetrating, 1086-1100
penetrating, 966-971
Aortic arch syndrome, *311*
Aortic-caval fistula, lanatoside C in, *474*
Aortic sinus aneurysms, unperforated, roentgen signs of, *625*
Aortic valve, *See* Valves
Aortitis
with aortic valve insufficiency in rheumatoid arthritis, *311*
syphilitic, bacterial endocarditis with, *1146*
Aortography
abdominal, complications of, *988*
complications of, *987*
retrograde, in mitral and aortic insufficiency, *987*
thoracic, *987*
Apex impulse, *303*
Apnea in curarized dogs, heart rate in, *474*
Arrhythmias
in electroconvulsive therapy, *152*
in penetrating heart wounds, 965
Arterenol. *See* Epinephrine and Norepinephrine
Arteries
of abdomen and pelvis, roentgenology of, *986*
calcification, in infancy, *309*
carotid
perfusion in cardiac by-pass, *628*
pulsatory expansion of wall, drugs affecting, *617*
coronary. *See* Coronary arteries
dilution curve with blockage of abdominal aorta, hypoxia and hemorrhage, *475*
diseases of small arteries and arterioles, 161-163
elasticity of large arteries, *620*
iliac, occlusion of, resection and grafting for, *442*
muscle contraction, 746-749
occlusion, acute, 512-524
oxygen saturation in myocardial infarction, *300*
peripheral, *150*, 512-524
pulmonary
absence of hypoplasia, unilateral, 557-565
aneurysm, *305*, 424-427
anomalies, bronchial obstruction from, 418-427
in mitral stenosis, 567-574, *620*
occlusion of, massive, 60-64
pressure in mitral valve disease, roentgen signs of, *625*
sclerosis, complicated, *462*
stenoses, 55-59, *461*
arterial oxygen in, *462*
with dextrocardia, 266-270
levarterenol affecting, *982*
renal
diameter of ostia of, *306*
occlusion in hypertension, *616*
sphygmography in arterial disease of lower extremities, *468*
Arterioles
diseases of, 161-163
neurogenic tone in hypertension, 798-805
Arteriovenous
admixture in polycythemia, 1029-1033
coronary fistula, *302*, 372-389
pulmonary shunt, *143*
Arteriovenous-like communications, coronary, 1001-1005
Arthritis, rheumatoid, aortic valve insufficiency in, aortitis with, *311*
Ascorbic acid
concentrations, related to age, *470*
effects on cholesterol atherosclerosis, 100
Atheromatous embolization, and pancreatitis, *1140*
Atherosclerosis, *974*, *1137-1139*
and alimentary lipemia, *974*
cholesteremia and nicotinic acid, *1137*
coronary
intramural hemorrhage in, 907-911
serum and urine studies in eunuchs, 1076-1084
in diabetes, lipid measures in, 14-21
epinephrine and serum lipid levels, *1137*
experimental, with cholesterol, 99-113
fasting and carbohydrate ingestion affecting serum lipids, *974*
fat ingestion affecting serum lipids, *974*
fatty meal affecting blood vessels, *1139*
focal lesions in, *1138*
genetic aspects of, *1139*
in Guatemala and New Orleans, *1138*
and hemophilia, *265*
hypothyroidism affecting, *1139*
pathogenesis of, *1137*
pregnancy protecting against, *974*
psychosomatic origin of, 1
quantitative appraisal of, *1138*
stress factors in, 852-860
thrombosis with, 488
Atria
biopsies during mitral commissurotomy, *980*
cor triatriatum sinister, *299*
electrokymogram, *1145*
epinephrine affecting rhythm in heart-lung preparation, *982*
gallop rhythm, 1007-1011
left
canalized thrombus of, *141*
electrokymography in mitral insufficiency, 213-223
hypertrophy in mitral stenosis, 567-574
measurement of pressure in, 199-203, 354-358
right, electrocardiographic signs of enlargement, 882-889
septal defects, *148*
in aged, *299*
with anomalous right pulmonary venous drainage, *976*
congenital, *975*
diagnosis of, *427*, *462*
electrocardiography in, *148*
phonocardiography in, *465*
surgery in, *203*
test for, *427*
size of, after surgery for patent ductus arteriosus, 1048
Atrial coronary arteries, 90-98
Atrioventricular bundle lesions
electrocardiography in, *1146*
with paroxysmal atrial tachycardia, *1145*

and ventricular septum defects, 271-275
Atropine, effects on heart, *981*
Autonomic nervous system
control of blood flow in hind paw of dog, *474*
and hypertension, *616*
and lung disease, *984*
vasoregulatory reflexes affecting sodium and water excretion, *983*

Bahamas, hypertension in, *729*
Ballistocardiography, *467*
correlated with hemodynamic data, *614*
in ectopic beats, *613*
of isolated heart, *614*
in overweight young adults, 87-89
after smoking, 451
Bantus, serum lipids in, 1021-1027
Barker lecture, 487-495
Baroceptor
activity in hypertension, 785-789, 791-797, *1149*
responses to rhythm changes, *304*
Blood flow
coronary, and hypoxemia, *464*
in foot, after sympathectomy and motor denervation, *474*
in hind paw of dog, autonomic control of, *474*
in infusion of adenylic acids, *154*
in myocardial infarction, *615*
venous, slowing of, thrombosis with, *488*
Blood nitrate levels, 1041-1046
Blood pressure
apparatus for measurements, *614*
drugs influencing, 208-212
fall of, in myocardial ischemia, *1146*
in heart
left atrial pressure measurement, 354-358
after rapid fluid injections, *308*
hypertension, *149-150*, *469-470* *616*, *1147-1150*
adrenal factors in, 743-744, 768-770, 771-781
aldosteronism with, *470*
aorta and smooth muscle electrolytes in, *1148*
capillaries in, *616*
carotid sinus activity in 785-789, 791-797, *1149*
conference on, 641-831
coronary insufficiency in, *1148*
and coronary occlusion, *242*
desoxycorticosterone affecting, *980*
in diabetes, lipid measures in, 17
diagnosis from renal artery occlusion, *616*
electrocardiogram in, cerebral centers affecting, *1148*
electrolyte factors in, 576-581, 746-749, 768-770, 771-781, *1149*, *1150*
environmental factors in, 728-741
epinephrine in, reversal of effects of, *470*
epinephrine sensitivity of peripheral vessels in, *150*
essential
neural factors in, 782-784
water and salt excretion in, *1149*, *1150*
experimental
effects on activity, *469*
kidney in, *475*
genetic factors in, 728-741
hypertensin, properties of, 664-667
inulin space in, *150*
ischemic ulcers with, 163
magnesium levels in, 761-763
malignant
medical therapy of, *1150*
total adrenalectomy for, *469*
mechanisms of
additive, 766
basic, 641
permissive, 765
reciprocal, 766
sensitizing, 766
nervous system in, autonomic, *616*, *984*
neural control of circulation in, 815-823
neural factors in, 811-814
neurogenic arteriolar tone in, 798-805
neurohumoral factors in, *1149*
new medical treatment of, *470*
8 - (para-aminobenzyl) - caffeine in, *149*
paradoxical, after aortic resection, *616*
pentolinium therapy, serum cholesterol in, 176-179
perfusion experiments, 798-801
pheochromocytoma
in children, *150*, *1150*
norepinephrine in, *1147*
pharmacologic tests in diagnosis of, *1148*
portal, blood vessels of liver and esophagus in, *310*
protective action of kidney, 719-727
protoveratrine in, *1147*
psychic trauma in, *616*
pulmonary
autonomic nervous system in, *984*
denervation affecting, *302*
long-lasting experimental, *1148*
in mitral stenosis, roentgenology in, *986*
primary, *305*, *984*
solitary, *149*
after surgery for patent ductus arteriosus, 1052
vascular patterns in, *305*
pulsatile flow and renin release, 681, 686
pyelonephritis with, 243-248
renal
adrenal cortex in, 765-767
experimental, *475*, 642-647
humoral mechanism of, 672-675, 708-712
pressor polypeptides and, 668-671
pressor system in, 658-663, 683-692
pyelonephritis with, 243-248
reduction by kidney perfusion, 702-707
related to renoprival hypertension, 719-727
renotrophin causing, 696-700
salt preference threshold of rats in, *469*
sustained, pathogenesis of, 653-657
renal factors in, 676-681
renin antibodies, 648-657
renoprival, 714-718
adrenal cortex in, 765-767
related to renal hypertension, 719-727
renotrophin causing, 696-700
single ischemic kidney, 689
Skelton type of, 768
sodium chloride affecting, 750-759, 768
sodium intake in, *150*
sodium levels in, 761-763
sympathetic activity in, 785-789
from thrombosis, aortic, *1149*
urologic aspects of, 693-695
vascular reactivity in, 807-810
vectorcardiogram in, *466*
hypotension
cerebral hemodynamics in, *303*
hemorrhagic, dextran in, *154*
heparin producing, *469*
from nitroglycerin, 1118
renal hemodynamics in, *303*
hypotensive drugs affecting kidney, *623*
in muscular dystrophy, 584
occlusion, arterial pressure after, *1149*
physical aspects of, *304*
pitressin and epinephrine affecting, *471*
pulmonary
long-lasting experimental, *1148*
primary, *305*, *984*
solitary, *149*
vascular patterns in, *305*
Blood supply
in exercise, *982*

Blood supply (*Cont'd*)
of interventricular septum, 391-396
Blood vessels. *See also* Arteries *and* Veins
cerebral vascular accidents and glutamic-oxalacetic transaminase activity, *145*
esophageal, in liver disease with portal hypertension, *310*
fatty meal affecting, *1139*
heparin affecting vascular healing, *460*
intrathoracic, transmural pressures in, *154*
of liver, in liver disease with portal hypertension, *310*
obstructive disease, collateral circulation in, *986*
peripheral
epinephrine sensitivity of, in hypertension, *150*
occlusive disease, 512-524
pressure pulses, interpretation of, 481-483
pulmonary
engorgement, *473*
hexamethonium affecting resistance, *992*
patterns in pulmonary hypertension, *305*
after surgery for patent ductus arteriosus, 1048
wedge pressure in, 199-203
reactivity in hypertension, 807-810
replacement of, *627*
responses to local cold injury, *983*
sling, vascular, 418-422
sympathectomy in Raynaud's disease, 5-13
Taussig-Bing complex, *300*
thrombosis, 487-495
transposition of great vessels, corrected, 249-254
Blood volume, pulmonary, in heart failure, *1142*
Book reviews
Les Angors Coronariens Intriques *(Froment and Gonia)*, 135
La Balistocardiographie *(Desruelles and Merlen)*, 134
Clinical Physiology *(Grollman)*, 134
The Coronary Club *(Faulkner)*, 140
Coronary Heart Disease *(Plotz)*, 136
Diagnosis and Treatment of Vascular Disorders *(Samuels, ed.)*, 138
Diseases of the Heart *(Friedberg)*, 139
New Bases of Electrocardiography *(Sodi-Pollares)*, 133
Pediatric Cardiology (*Nadas*), 136
Radicular Syndromes *(Davis)*, 139
Roentgen Signs in Clinical Diagnosis *(Meschan)*, 140
Röntgenologische Funktionsdiagnostik *(Janker)*, 140
The Shoulder and Environs *(Bateman)*, 137
Synopsis of Pathology *(Anderson)*, 139
Venous Return *(Brecher)*, 133
Bradycardia
in myocardial infarction, 1115
sodium lactate in, *1145*
Bradykinin, 669
Breathing, periodic, pulmonary compliance in, 1056-1061
Brock's operation in pulmonary stenosis, *462*
Bronchial arteries
in angiocardiogram, 563
obstruction from pulmonary artery anomalies, 418-427
Bronchoscopic method of measuring left atrial pressure, 354-358
Bundle, atrioventricular, and ventricular septum defects, 271-275
Bundle-branch block
with cardiomegaly, *1146*
electrocardiography in, *978*
experimental, ventricular excitation in, *979*
masquerading, 397-408

C-reactive protein, in myocardial necrosis, *302*
Caffeine, effects on cholesterol atherosclerosis, 105
Calcification
arterial, in infancy, *309*
of ascending aorta, *624*
Calcium-digitalis tolerance test, *1152*
Camphidonium, *1153*
Capillaries
alveolar-capillary block syndrome, *314*
in hypertension, *616*
pressure, pulmonary, and wedge pressure, 199-203
Carbohydrate ingestion, effects on serum lipids, *974*
Carbon dioxide
in emphysema, 1117
sensitivity of respiratory center to, *981*
Carbonic anhydrase
activity in respiratory disease, *470*
inhibition, *981*, *983*
Cardiovascular conditions. *See also* Blood vessels *and* Heart
complications in diabetes, lipoprotein and cholesterol in, 14-21
emergencies, prevention and management of, 1112-1122
reactivity after hepatectomy, *982*
status of normal newborn, 303
Carotid artery
perfusion in cardiac by-pass, *628*
pulsatory expansion of wall, drugs affecting, *617*
Carotid sinus
activity in hypertension, 785-789, 791-797
constriction, hypertension from, *1149*
Castration, male, serum and urine studies after, 1076-1084
Catheterization, cardiac
of coronary sinus and veins, complications in, *979*
electrode catheter in diagnosis of Ebstein's disease, 543-548
and exercise test, *475*
hemodynamic data from, *980*
intracardiac electrocardiograms and phonocardiograms with, *1144*
left-heart
technic of, *615*
in mitral insufficiency, 213-223
in mitral stenosis, 567-574
in muscular dystrophy, 583-588
of pulmonary veins and left heart of dog, *1145*
retrograde, in mitral and aortic insufficiency, *987*
in unilateral pulmonary artery absence, 557
Cerebral
abscess, with congenital defects, *299*
aneurysms, in pregnancy, *311*
angiomatous malformation, 1127
hemodynamics in hypotension, *303*
impedance changes after circulatory arrest, *622*
ischemia, cardiac output in, *304*
vascular accidents and glutamic-oxalacetic transaminase activity, *145*
Cesium, action of, *621*
Cheyne-Stokes breathing, mechanism, of, 1056
Chilblains, chronic, *162*
Childhood conditions. *See* Pediatrics
Chloral hydrate, effects on cholesterol atherosclerosis, 104
Chlorpromazine
effects on antidiuretic hormone, *985*
effects on myocardial hypoxia, *152*
Cholesterol
atherosclerosis, experimental, 99-113
in Bantu and white subjects, 1021-1027
cholesteremia and nicotinic acid, 497-504, *1137*
determination of, 948
in diabetic patients, 14-21
hereditary and environmental factors, 537-541

in myocardial infarction, *463*
in pentolinium-treated hypertension, 176-179
pericarditis, cholesterologenic, *146*
in stress, 852-860
Choline, effects on cholesterol atherosclerosis, 104
Circulation time determinations, 922-925
during exercise, *982*
Coagulation and thromboembolism, *141-142*, *460-461*, *612-613*, *974-975*, *1139-1140*
anticoagulants
in angina pectoris, *463*
in arterial occlusion, 520
in atherosclerosis, cholesterol, 106
in coronary artery disease, 948
long-term therapy, *1140*
in mitral disease, *975*
in myocardial infarction, *672*
in pregnancy, 1118
resistance to tissue thromboplastin, *141*
in thrombosis, 491
antihemophilic factor, storage of *612*
electron microscope studies, *1139*
embolism
arterial, in mitral stenosis and commissurotomy, *988*
atheromatous, and pancreatitis, *1140*
in penetrating heart wounds, 961
in pregnancy, 1118
pulmonary, 60-64, *141*
fats, postpranial effects of, *141*, 936-940
fragmentation of clots, 518
heparin affecting vascular healing, *460*
in hypothermia and cardiac surgery, *461*
and lipemia, alimentary, 927-934, *974*
lysis of clots, 518
plasma lipids and coagulation, *612*
prothrombin time, postoperative, *460*
pulseless disease, *311*, *975*
stress and blood clotting, 852-860
thrombosis, 487-495
and alimentary lipemia, *974*
aortic
hypertension from, *1149*
primary, 941-944
atrial, canalized, *141*
coronary. *See* Coronary arteries
hypercoagulability and, 488
massive intracavitary cardiac, *975*
portal vein, *613*
of pulmonary artery, 60-64
in trauma
of aorta, 968
of heart, 961
tromexan therapy, *1140*
Coarctation, aortic. *See* Aorta
Cold injury
inositol and rewarming in, *983*
sequelas to, *311*
temperature changes after, *621*
vascular responses to, *983*
Collateral circulation
coronary, exercise affecting, *301*
formation in limbs, 518
in obstructive arterial disease, *986*
Commissurotomy, mitral
arterial embolism in, *988*
atrial biopsies during, *980*
cardiorespiratory function two years after, *993*
effects of aortic valve lesions, *627*
hemodynamics in, *992*
indications for, *994*, 1114, 1121
phonocardiography before and after, *614*
postcommissurotomy syndrome, 549
in pregnancy, 204-207, *988*, 1121
roentgenology after, *986*
Conduction system
anatomic studies of, 271-275
defects in pentrating heart wounds, 965
Congenital anomalies, *142-143*, *299-300*, *461-462*, *975-977*, *1141-1142*
aortic coarctation
reverse syndrome, *299*
splanchnic circulation with, *1142*
aortic stenosis
outlook for children with, *992*
surgery for, *1116*
arteriovenous pulmonary shunt, ***143***
atrial septal defects, *975*
in aged, *299*
cerebral abscess with defects, *299*
cor triatriatum sinister, *299*
coronary artery anomalies, *976*
1062-1068
corrected transposition of great vessels, 249-254
dextrocardia. *See* Dextrocardia
Ebstein's disease, *142*, 543-548, *977*, *1141*
exercise affecting left-to-right shunt, *1142*
heart block, *276*
induced, in rats, survival after, *300*
Marfan's syndrome, *1141*
patent ductus arteriosus. *See* Patent ductus arteriosus
pulmonary artery stenoses, *461*
survival with, *462*
pulmonary venous drainage, right, anomalous, *976*
splenic agenesis and cardiac abnormalities, 72-83, *142*
Taussig-Bing complex, *300*
tetralogy of Fallot, pregnancy in, *142*
venous return to heart, anomalous, *975*
ventricular septal defects, *1141*
with aortic coarctation, and pulmonary sclerosis, *462*
surgery for, *143*
Conner Memorial Lecture, 842-850
Contractile force measurements, *621*
Contraction, arterial muscle, 746-749
Cor pulmonale, 164-174
gastroduodenal disease with, *313*
sensitivity of respiratory center to carbon dioxide in, *981*
Cor triatriatum sinister, *299*
Coronography, in anastomoses between coronary arteries, *978*
Coronary arteries, *143-146*, *300-302*, *977-978*, *1143*
anomalies, 1001-1005
of left artery, 1062-1068
unusual, *976*
anticoagulants
in angina pectoris, *463*
in myocardial infarction, *612*
arterial oxygen saturation in myocardial infarction, *300*
arteriovenous fistula, *302*, 372-389
arteriovenous-like communications, 1001-1005
atrial 90-98
blood flow in myocardial infarction, *615*
bradycardia in myocardial infarction, 1115
C-reactive protein in myocardial necrosis, *302*
cardio-omentopexy in coronary insufficiency, *464*
cholesterol levels in myocardial infarction, *463*
coronography of anastomoses, *978*
death from disease, manner of, *301*
defibrillation in acute occlusion, *270*
diagnostic aids in myocardial infarction, *977*
distribution of thrombosis attacks, *144*
EDTA in angina pectoris, *301*
enzyme changes in myocardial infarction, *151*, *977*
epidemiology of disease, 321-324
eunuchs, serum and urine studies in, 1076-1084
exercise affecting collateral circulation, *301*
fibrinogen and sedimentation rates in disease, *301*
glutamic-oxalacetic transaminase in myocardial infarction, *145*, *464*

Coronary arteries (*Cont'd*)
hemorrhage, intramural, in atherosclerosis, 907-911
hypertension and coronary occlusion, *242*
hypoxemia and coronary blood flow, *464*
infarction, *144*
inflammatory changes, *464*
injuries, 959
Israel, myocardial infarction in, *463*
long-term management of patients, 945-952
Manvene in diseases, 1035-1040
mortality statistics in disorders, *1143*
perfusion, in cardiac by-pass, *628*
in pregnancy, *1143*
prognosis in myocardial infarction, *300*, *465*
progress in field of disorders, *302*
reflexes, intercoronary, *143*
resection for ventricular aneurysm, *144*
roentgenography of, *624*
stress factors in disease, 1-3, 852-860
surgical treatment of disease, *144*
two-step exercise test, *143*
women, myocardial infarction in, *145*
work capacity with old myocardial infarction, *464*
Coronary sinus and veins
catheterization of, complications in, *979*
retrograde perfusion of, *988*
Cortisone, in Paget's disease, effects on cardiac output, *470*
Coumarin compounds, in thrombosis, 492
Cysts, hydatid, of heart, 127-131

Death
in coronary artery disease, *301*
from overexertion in animals, *304*
Decholin circulation time, 922-925
Defibrillation
in coronary occlusion, *270*
electric shock in, *303*
Delta wave, in Wolff-Parkinson-White syndrome, 225-231
Demerol, effects of, 1119
Denervation
foot blood flow after, *474*
lung, affecting pulmonary hypertension, *302*
Dental extractions, and bacterial endocarditis, *616*
Dermofluorographic circulation time, 922-925
Desoxycorticosterone
action of, *623*
effects in hypertension, *980*
Deuterium oxide equilibration in edema, *983*

Dextran
in hemorrhagic hypotension, *154*
in thrombosis, 491
Dextrocardia
pulmonary stenosis with, 266-270
pulmonary vein transposition and partial agenesis of lung with, *462*
venous ventricle hypertrophy in, *466*
Diabetes
cholesterol in, 14-21
lipoprotein in, 14-21
transmetatarsal amputation in, *990*
Diamox, affects of, *983*
Diastolic filling of beating excised heart, *622*
Dibenzyline, effects of, *981*
Dicumarol
in angina pectoris, 348-352
in atherosclerosis, cholesterol, 107
harmful effects on fetus, 1119
resistance to tissue thromboplastin, *141*
in thrombosis, 491
Dietotherapy, in coronary artery disease, 947
Digitalis
calcium-digitalis tolerance test, *1152*
effects on myocardium in potassium deficiency, *984*
glycosides injected into lateral ventricle of brain, *152*
preoperative use of, *1114*
toxicity
in infancy and childhood, *1152*
quinidine in, 1114
Digoxin, in atrial fibrillation, *473*
Diuretics
antidiuretic effect of chlorpromazine, *985*
antidiuretic effects of sedatives, 1119
osmotic, in edema, 1013-1019
oral, nonmercurial, 918-921
Rolicton, *472*
Diverticulum of mitral valve, *993*
Ductus arteriosus
of newborn, *303*
patent. *See* Patent ductus arteriosus
persistent, phonocardiography in, *466*
Ductus Botalli, persistent, with complication, *462*

Ebstein's disease, *142*, *977*
diagnosis of, *1141*
electrode catheter in diagnosis, 543-548
Echinococcus disease of heart, 127-131
Ectopic beats, ballistocardiography of, *613*
Edema
equilibration of drugs in, *983*
of limbs, *309*
pelvic etiology of, *309*
osmotic diuretic treatment of, 1013-1019
EDTA in angina pectoris, *301*
Effortil, effects of, *472*
Eisenmenger complex, roentgenology in, *625*
Elasticity of large arteries, *620*
Electric alternans
in single ventricular fibers, *622*
total, in pericardial disease, 912-917
Electric pacemaker stimuli, external, effects of, *626*
Electrocardiography
in acrosclerosis and sclerosis, 874-880
in aldosteronism, *1145*
in angina with mitral disease, *994*
in anxiety, 1122
atrial
in enlargement, right, 882-889
in fibrillation, *979*
in septal defect, *148*
in tachycardia, paroxysmal, with atrioventricular block, *1145*
in atrioventricular bundle lesions, *1146*
in bundle-branch block, *978*
masquerading, 397-408
in cardiomegaly with bundle-branch block, *1146*
in cor pulmonale, 164-174
in emotional stress, 1119
factors influencing, *613*
fetal, *613*
Frank precordial lead system, 1069-1075
in hypothermia, *146*
intracardiac catheterization with, *1144*
leads, theory of, *465*
in mitral insufficiency, *468*
in muscular dystrophy, 583-588
in myocardial destruction, *147*
after nitrites for angina pectoris, 31, 35
normal orthogonal, 1102-1110
in paralysis, familial periodic, *1145*
phonocardiography with, *418*
polarity of ST vector, *979*
postextrasystolic sinus beat, *467*
and potassium metabolism, *1145*
in pseudoventricular rhythms, *147*
QS deflections in right-sided precordial leads, *1144*
radiation reactions in heart, *147*
after smoking, 450
suspended heart syndrome, *149*
in thiamine-deficient baby pigs, *618*
after thoracic surgery, *989*
in uremia, *614*
ventricular
excitation in experimental bundle branch block, *979*
gradient, *147*
hypertrophy
left, 255-264

right, *466*
tachycardias, differential diagnosis of, *467*
in wounds of heart, penetrating, 965
Electroconvulsive therapy, arrythmias in, *152*
Electrokymography
atrial, *1145*
in mitral insufficiency, 213-223
in myocardial ischemic, *1146*
quantitative, *1143*
Electrolyte effects on circulation, *305-306, 475, 984-986*
in hypertension, 576-581, 746-749, 768-770, 771-781, *1148, 1149, 1150*
desoxycorticosterone affecting, *980*
imbalance, and potassium-sodium exchange, *985*
pitressin and epinephrine affecting, *471*
Electroshock therapy
in defibrillation, *303*
in patients with cardiovascular disease, *314*
Embolectomy, 520
Embolism. *See* Coagulation and thromboembolism
Emergencies, cardiovascular, prevention and management of, 1112,
Emotional stress. *See* Stress
Emphysema
carbon dioxide with oxygen in, 1117
pulmonary, venesection in, *622*
response to straining, 65-70
sensitivity of respiratory center to carbon dioxide in, *981*
Endangiitis obliterans, *1137*
Endocardial fibroelastosis, angiocardiography in, 40-45
Endocarditis
bacterial
with coaretation of aorta and aneurysm of sinus of Valsalva, 432-442
and dental extractions, *616*
follow-up studies of patients, *1147*
pregnancy after, 1116
with syphilitic aortitis, *1146*
lenta, Wasserman and Kahn tests in, *980*
rheumatic subacute, latent, *980*
Endothelial disease, thrombosis from, 488
Energy requirements of work loads, 115
Environment
and hypertension, 728-741
and serum cholesterol, 537-541
Enzymatic changes in myocardial infarction, *145, 464, 977*
Epidemiology
in coronary heart disease, 321-324
in hypertension, 732
Epilepsy, and mitral stenosis, *310*
Epinephrine
and atrial rhythm in heart lung preparation, *982*
biosynthesis of, 366-370
and blood pressure and electrolytes, *471*
blood pressure responses to, under anesthetics, *153*
chlorpromazine affecting, *980*
and denervated heart in unanesthetized dogs, *474*
dibenzyline affecting, *981*
hemodynamic effects of, *471*
hypertensive effects of, reversal of, *470*
isopropylnorepinephrine in complete heart block, 526-536
and lipid levels of serum, *1137*
muscle response to, 746-749
norepinephrine. *See also* Levarterenol
and atrial rhythm in heart-lung preparation, *982*
biosynthesis of, 366-370
and cardiac output in anesthetized dogs, *619*
chlorpromazine affecting, *980*
and circulation, pulmonary, *472*
circulatory effects of, *472*
dibenzyline affecting, *981*
effects of, 208-212
in pheochromocytoma, *1147*
and radioboron uptake, *152*
Regitine affecting, *980*
in urine, *151*
and ventricular performance, *1152*
and pulmonary circulation, *472*
Regitine affecting, *980*
sensitivity of peripheral vessels in hypertension, *150*
in Stokes-Adams disease, 325
in urine, *151*
and ventricular performance, *1152*
Erythrocyte sedimentation rate
in myocardial infarction, *301*
in rheumatic fever, *986*
Erythrol tetranitrate in angina pectoris, 23-36
Eskimos, hypertension in, 739
Esophagus, blood vessels of, in liver disease with portal hypertension, *310*
Estrogen, new analog in coronary heart disease, 1035-1040
Eunuchs, serum and urine studies of, 1076-1084
Exercise
and cardiac catheterization, *475*
cholesterol atherosclerosis in, 110
circulation times and blood distribution during, *982*
collateral coronary circulation during, *301*
death from overexertion in animals, *304*
left-to-right shunt during, *1142*
two-step test, *143*
ventilatory response to, in mitral stenosis, *992*
Extremities
acute arterial occlusion of, 512-524
circulation in forearm, *474*
edema of legs, *309*
foot blood flow after sympathectomy, *474*
ischemic toes, oscillating bed for, 277-282
lymphatic vessels in, *314*
transmetatarsal amputation in diabetes, *990*
Eye changes in pulseless disease, *311*

Familial conditions. *See* Heredity
Fasting, effects on serum lipids, *974*
Fat ingestion
blood coagulation after, 936-940
blood vessels after, *1139*
and mortality from heart disease, *4*
postprandial effects of eating, *141*
serum lipids after, *974*
Femoral vein, strain obstruction syndrome of, *307*
Fetus
Dicumarol affecting, 1119
electrocardiography of, *613*
Fibrillation
atrial
from acetylcholine, in hypopotassemia, *472*
digoxin in, *473*
electrocardiography in, *979*
quinidine in, 1113
and procaine amide, *1152*
in sleep, 1115
pseudoventricular, *147*
ventricular
defibrillation in coronary occlusion, *270*
drugs for, 1117
electric shock in defibrillation, *303*
with hypothermia, procaine amide in, *1151*
Fibrin formation, electron microscope studies of, *1139*
Fibrinogen levels in myocardial infarction, *301*
Fibrinolysins, 493, 521
intravenous protein-free pyrogens, 187-197
Fibroelastosis, endocardial, angiocardiography in, 40-45
Fick method of cardiac output estimate, 585
Fistula
aortic-caval, lanatoside C in, *474*
arteriovenous coronary, *302,* 372-389
Fluorohydrocortisone, cardiotonic activity of, *617*
Fluoroscopy after surgery for patent ductus arteriosus, 1052

Foot blood flow after sympathectomy and motor denervation, *474*
Forearm, circulation in, *474*
Foreign bodies in heart, retained, 956-959
Frank lead systems, 46-54, 1069-1075

Gallop
atrial, 1007-1011
ventricular, in mitral stenosis, *982*
Ganglionic-blocking agent, *1153*
Gangrene
of extremities, *309*
paradoxic, after lumbar sympathectomy, *312*
Gastric secretion, basal, reserpine affecting, *618*
Gastroduodenal disease with cor pulmonale, *313*
Genetic conditions. *See* Heredity
Glucose, effects on papillary muscle, *622*
Glutamic-oxalacetic transaminase activity in myocardial infarction, *145*, *464*, *977*
Glutaminase, renal, Diamox affecting, *983*
Glycerol trinitrate. *See* Nitroglycerin
Glycoproteins, serum, in eunuchs, 1076-1084
Glycosides
cardiac, in traumatic shock, *151*
digitalis, injected into lateral ventricle of brain, *152*
Gonadotropine, urinary, in eunuchs, 1076-1084
Grafts, blood vessel, *627*
in occlusion of aorta or iliac arteries, *442*
in thrombosis, 494
Guatemala, atherosclerosis in, *1138*

Harvey, William, 428-431
Heart
abnormalities, and splenic agenesis, 72-83, *142*
anatomic studies of conduction system, 271-275
anesthesia in disease, 292-298
apical impulses, *303*
arrest
management of, *988*, *989*
with potassium citrate, *1151*
atrial disorders. *See* Atria
block
complete hemodynamic functions in, 526-536
congenital, *276*
cardioangiography. *See* Angiocardiography
cardiomegaly
with bundle-branch block, *1146*
familial, *990*
cardio-omentopexy in coronary insufficiency, *464*
cardiorespiratory
function after mitral commissurotomy, *993*
syndrome of obesity, *313*
cardiothoracic ratio after surgery for patent ductus arteriosus, 1047
cardiotropic substance, absence of, in coronary sinus blood of dogs, *472*
cerebral abscess with congenital defects, *299*
damage in hypothermia, *175*
dextrocardia. *See* Dextrocardia
distensibility and contractility of frog heart, *154*
echinococcus disease, 127-131
endocardial fibroelastosis, 40-45
endocarditis. *See* Endocarditis
failure, *462*, *1142-1143*
acetyldigitoxin therapy, *462*, *978*
hydrothorax in, *463*
latent, in muscular dystrophy, 583-588
pathologic changes in, *1142*
prognosis, *1143*
pulmonary blood volume in, *1142*
right-sided, aldosterone activity in, *151*
and glutamic-oxalacetic transaminase activity, *145*
molar sodium lactate effecting function, *305*
mortality from disease, and fat in diet *4*
myocarditis. *See* Myocarditis
in myxedema, *981*
nitrous oxide test in left-to-right shunts, 284-290
output
in cerebral ischemia, *304*
Fick method of estimating, 595
in muscular dystrophy, 585
norepinephrine affecting, in anesthetized dogs, *619*
in Paget's disease, cortisone affecting, *470*
regulation of, *994*
pericarditis. *See* Pericarditis
pressure changes after rapid fluid injections, *308*
pulmonary heart disease, 164-174, *313*, *981*
rate, in apnea in curarized dogs, *474*
rehabilitation of patient, 114-126
rhabdomyosarcoma of, *990*
rheumatic disease, 842-850. *See also* Rheumatic heart disease
transmural pressures in, *154*
trauma, 953-966
uncommon forms of disease, *990*
unknown disease in siblings, *990*
valvular disease *991-994* *See also* Valves
ventricular disorders. *See* Ventricles
Heart-lung apparatus in surgery, *989*
Heart-lung preparation, epinephrine affecting atrial rhythm in, *932*
Helm system of vectorcardiography, 46-54
Hematoma, spontaneous intracerebral, 1127
Hemophilia, with atherosclerosis, *265*
Hemoptysis, in pregnancy, mitral commissurotomy in, 204-207
Hemorrhage
adrenal bilateral, in anticoagulant therapy, 1117
aortic intimal, 1090
arterial dilution curve in, *475*
intracranial, subarachnoid, spontaneous, 1123-1135
intramural, in coronary atherosclerosis, 907-911
in penetrating injury of aorta, 968
retroperitoneal, *308*
Hemorrhagic hypotension, dextran in, *154*
Heparin
and cholesterol atherosclerosis, 106
hypotensive action of, *469*
resistance to tissue thromboplastin, *141*
in thrombosis, 491
and vascular healing, *460*
Hepatectomy, cardiovascular reactivity after, *982*
Heredity
and atherosclerosis, *1139*
cardiomegaly, familial, *990*
with bundle-branch block, *1146*
and hypertension, 728-741
and serum cholesterol, 537-541
Hexamethonium
and pulmonary vascular resistance, *992*
and reserpine therapy, *623*
vascular reactivity after, in hypertension, 807-810
Histamine, effects on pulmonary circulation, *472*
Hydatid disease of heart, 127-131
Hydrothorax, in heart failure, *463*
Hypertensin
nature of, 658-663
synthesis and properties of, 664-667, 668
Hypertensinogen formation, 765
Hypertension, Hypotension. *See* Blood pressure
Hyperventilation, circulatory studies in, *983*
Hypophysectomy, hemodynamics after, *620*
Hypopotassemia, *291*
atrial fibrillation in, from acetylcholine, *472*
Hypothalamus, affecting hypertension, 782
Hypothermia
coagulation in, *461*
electrocardiography in, *146*
heart damage in, *175*

ventricular fibrillation with, procaine amide in, *1151*
Hypoxemia, and coronary blood flow, 464
Hypoxia
arterial dilution curve in, *475*
myocardial, chlorpromazine affecting, *152*

Ibogaine, cardiovascular action of, *471*
Iliac arteries, resection and grafting for occlusion, *442*
Indandione compounds, in thrombosis, 492
Industry, cardiac patient in, 119
Infancy. *See* Pediatrics
Infarction, myocardial. *See* Coronary arteries
Infection in penetrating heart wounds, 962
Inhibition, protective, in coronary insufficiency with hypertensive disease, *1148*
Inositol, effects after cold injury, *983*
Inulin space, in hypertension, *150*
Iodine
in hypertension, *470*
radioactive
in angina pectoris, 949
in paroxysmal tachycardia, 900-906
Ischemia
acute arterial occlusion, 512-524
cerebral, cardiac hemodynamics in, *304*
of kidney, single, 689
myocardial, fall of blood pressure in, *1146*
of toes, oscillating bed for, 277-282
Isopropylnorepinephrine, in complete heart block, 526-536
Isoproterenol, in Stokes-Adams disease, 325
Israel, myocardial infarction in, *463*

Japan, hypertension in, 738

Kahn test in endocarditis lenta, *980*
Kallidin, 669
Ketosteroids, urinary, in eunuchs, 1076-1084
Kidneys
aminoaciduria, *623*
biopsies in toxemia of pregnancy, *985*
effects on circulation, *305-306, 475, 623, 984-986*
horseshoe, abdominal aortic aneurysm with, *308*
in hypertension, 676-681. *See also* Blood pressure, hypertension, renal
in hypotension, *303 See also* Blood pressure, hypotension, renal
hypotensive drugs affecting, *623*
potassium deficiency and, *623*
protective action of, 719-727
Scillaren B affecting function, *991*
serotonin affecting hemodynamics of, *986*
in shock treated with levarterenol, *371*
single ischemic, 689
sodium lactate affecting metabolism in disease, *306*
transplants in twins, 707
Kimmelsteil-Wilson syndrome, in diabetes, lipid measures in, 17

Laceration of aorta, 1086
Lactic dehydrogenase, serum, alterations in myocardial infarction, *977*
Lanatoside C, in aortic caval fistula, *474*
Legs, edema of, *309*
pelvic etiology of, *309*
Levarterenol. *See also* Epinephrine and norepinephrine
in pulmonary stenosis, *982*
in renal changes in shock, *371*
in Stokes-Adams disease, 325
Ligation
deep vein, in postphlebitic extremity, *310*
in thrombosis, 494
Lipemia, alimentary, and blood coagulation, 927-934, *974*
Lipids. *See also* Cholesterol
plasma, and coagulation of blood, *612*
serum
in Bantu and white subjects, 1021-1027
epinephrine affecting, *1137*
in eunuchs, 1076-1084
fasting and carbohydrate ingestion affecting, *974*
fat ingestion affecting *974*
in Manvene therapy, 1035-1040
plant sterols and vegetable oils affecting, 890-898
in stress, 1117
Lipoprotein, in diabetic patients, 14-21
Livedoreticularis, 162
Liver
blood vessels of, in liver disease with portal hypertension, *310*
pulsations in tricuspid insufficiency, *994*
Lungs
agenesis, partial, with dextrocardia, *462*
blood volume in heart failure, *1142*
compliance
in cardiac disease, *622*
in periodic breathing, 1056-1061
cor pulmonale, 164-174, *313 981*
denervation affecting pulmonary hypertension, *302*
diffusion capacity of, *314*
diseases, *305, 622, 983-984*
drugs affecting circulation, *472-991*
embolism, *141*
emphysema, Valsalva maneuver in, 65-70
function studies in pulmonary artery absence, 564
hypertension. *See* Blood pressure, hypertension, pulmonary
methonium in disease, *622*
nervous system, autonomic, in disease, *984*
ossification with mitral stenosis, *994*
pulmonary-thoracic ratio, after surgery for patent ductus arteriosus, 1048
Scillaren B affecting circulation, *991*
spleen-lung ether time, *313, 1147*
venesection affecting pulmonary and cardiac function, *622*
Lymphatics
circulation studies, with radioactive plasma protein, *314*
function test, *309*
vessels in extremities, *314*

Magnesium
protective action in trauma, *621*
serum levels in hypertension, 761-763
Mannitol
in angina pectoris, 23-36
in edema, 1013-1019
Manvene, in coronary heart disease, 1035-1040
Marfan's syndrome, *1141*
aortic insufficiency with, repair in, *626*
Master two-step exercise test, *143*
Metabolic effects on circulation, *151, 470, 617, 981, 1151*
Metabolism, renal, sodium lactate affecting, in disease, *306*
Methonium, in pulmonary disease, *622*
Methoxamine, mechanisms of, *151*
Miners, circulatory studies in, *314*
Mitral valve. *See* Valves
Molar sodium lactate. *See* Sodium lactate
Mortality
in coronary artery disease, *1143*
in heart disease, and fat in diet, *4*
Murmurs
in children, *153*
aortic origin of, *153*
spectrophonocardiography in, *148*
systolic, 601-610

Muscles
electrolytes in hypertension, *1148*
vascular smooth muscle tonus, 746-749
Muscular dystrophy, 583-588
Myocardial extract, effects of, *1153*
Myocarditis
acute idiopathic, *468*
giant cell, *468*, *615*
granulomatous, *468*
in infancy, *1146*
postvaccinial, *615*
Myocardium
digitalis affecting, in potassium deficiency, *984*
hypoxia, chlorpromazine affecting, *152*
infarction. *See* Coronary arteries
necrosis, C-reactive protein in, *302*
revascularization, *628*
Myxedema, *981*

Negroes, hypertension in, 728
Neodicoumarin, effects on cholesterol, atherosclerosis, 106
Nephrectomy, in hypertension, 693
Nervous system
autonomic
control of blood flow in hind paw of dog, *474*
and hypertension, *616*
and lung disease, *984*
vasoregulatory reflexes affecting sodium and water excretion, *983*
sympathetic, affecting blood pressure, 785-789, 798-805
Neural control of circulation in hypertension, 815-823
Neural factors in hypertension, 782-784, 811-814
Neurogenic arteriolar tone, in hypertension, 798-805
Neurohumoral factors in hypertension, *1149*
New Orleans, atherosclerosis in, *1138*
Newborn, normal, cardiovascular status of, *303*
Nicotinic acid
in cholesteremia, *1137*
in hypercholesterolemia, 497-504
Nitrate levels in blood, 1041-1046
Nitrites, in angina pectoris, 22-37
Nitroglycerin
in angina pectoris, 22-36
effects of, 1041-1046
hypotension from, 1118
Nitroglyn, in angina pectoris, 23
Nitrol Ointment, in angina pectoris, 25-36
Nitrous oxide test, 284-290
Node, atrioventricular, and ventricular septum defects, 271-275
Norepinephrine. *See* Epinephrine
Nucleotides
levels in human cardiac muscle, *1151*
synthesis of, in heart muscle extracts, *1151*

Obesity, cardiorespiratory syndrome of, *313*
Occlusion
massive, of main pulmonary artery, 60-64
peripheral arterial, 512-524
renal artery, in hypertension, *616*
Open heart surgery, in pulmonic stenosis, 180-185
Orthogonal electrocardiogram and vectorcardiogram, 46-54, 1102-1110
Orthostatic circulatory disturbances, *473*
Oscillating bed, and circulation of ischemic toes, 277-282
Osmotic diuretics in edema, 1013-1019
Osseus phlebography, *987*
Ossifications, pulmonary, in mitral stenosis, *994*
Ouabain
action of, *619*
in heart block from drugs, *153*
Overweight young adults, ballistocardiogram in, 87-89
Oxygen
anoxia and cholesterol atherosclerosis, 107-110
arterial, in pulmonary stenosis, *462*
consumption
reserpine affecting, *617*
in thyroid disorders, *617*, *620*
hypoxia, *See* Hypoxia
saturation
arterial, in myocardial infarction, *300*
of venous blood, *283*
tension of ischemic toes, 277-282
therapy, in emphysema, 1117
Oxytocin, 669

Pacemaker stimuli, external electric, effects of, *626*
Paget's disease, cortisone affecting cardiac output in, *470*
Pancreatitis, and cardiovascular disease, *1140*
Papillary muscle, glucose affecting, *622*
8-(para-aminobenzyl)-caffeine in hypertension, *149*
Paralysis, family periodic, electrocardiography in, *1145*
Parasystole, intermittent, *467*
Paritol, in thrombosis, 491
Patent ductus arteriosus
angiocardiography in, *624*
and congenital aortic valvular disease, 359-365
hemodynamics of, *1141*
in infancy, *142*
with pulmonic stenosis, 232-241
radiology after, 1047-1054
simultaneous pressure studies in surgery, *1141*
systolic murmurs in, 608
Pathology, *1151*
Pediatrics
aortic stenosis in children, outlook for, *992*
arterial calcification in infancy, *309*
cardiovascular status of normal newborn, *303*
congenital anomalies. *See* Congenital anomalies
digitalis intoxication in infancy and childhood, *1152*
myocarditis in infants, *1146*
pheochromocytoma in children, *1150*
ventricular septal defects in infants, *1141*
Pelentan, effects on cholesterol atherosclerosis, 106
Pelvis
arteries of, roentgenology of, *986*
etiology of limb edema, *309*
Penicillin, in prophylaxis of rheumatic fever, 1113
Pentaerythritol tetranitrate (PETN)
in angina pectoris, 23-36
effects of, 1041-1046
Pentolinium
effects of, 208-212
in experimental renal hypertension, 646
in hypertension, serum cholesterol after, 176-179
Pepsanurin, 669
Pepsitensin, 668
Pepsitocin, 669
Perfusion
experiments in hypertension, 798-801
kidney, reducing hypertension, 702-707
retrograde, of coronary sinus, *988*
Pericardiectomy in chronic idiopathic pericarditis, *615*
Pericardiotomy, syndrome after, 549-555
Pericarditis
acute staphylococcal, *146*
cholesterologenic, *146*
chronic idiopathic, pericardiectomy in, *615*
constrictive
angiocardiography in, *306*, *307*
hemodynamic repercussions of, *469*
portal circulation in, *1147*
post-traumatic, *146*
radiologic aspects of, *224*
Pericardium
disease, total electric alternation in, 912-917
injury, 960
Periodic breathing, pulmonary compliance in, 1056-1061

Peripheral vessels
epinephrine sensitivity of, in hypertension, *150*
occlusive disease, 512-524
Peripherin, effects of, *472*
Peritrate. *See* Pentaerythritol tetranitrate.
Pernio, chronic, 162
Pharmacology, *151-153, 470-473, 617-619, 980-981, 1151-1153. See also specific drugs*
absence of vasoactive and cardiotropic substances in coronary sinus blood of dogs, *472*
anesthetics and blood pressure responses to epinephrine, *153*
drugs affecting pulmonary circulation, *472*
drugs affecting pulsatory expansion of carotid arterial wall, *617*
drugs affecting radioboron uptake, *152*
ouabain in heart block from drugs, *153*
sympathomimetic substances, effects on circulatory values, *472*
Phenamine, effects on cholesterol atherosclerosis, *103*
Phenindione, in thrombosis, 491
Phenobarbital, effects on cholesterol atherosclerosis, 103
Phenylephrine, in Stokes-Adams disease, 325
Pheochromocytoma
in children, *150, 1150*
norepinephrine in, *1147*
pharmacologic tests in diagnosis of, *1148*
Phlebitis, deep vein ligation in postphlebitic activity, *310*
Phlebography, osseus, *987*
Phonocardiography
in atrial septal defect, *465*
electrocardiography with, *148*
esophageal and precordial, *465*
intracardiac, with catheterization, *1144*
in mitral stenosis, *466, 614, 620, 978*
in persistent ductus arteriosus Botalli, *466*
Phospholipids, postprandial effects of eating, *141*
Physical fitness index. 117
Physiology, *154, 302-305, 473-475, 620-622, 982-983*
Pitressin
effects on blood pressure and electrolytes, *471*
effects on radioboron uptake, *152*
Pituitary, hemodynamics after hypophysectomy, *620*
Plasmin, in thrombosis, *493*
Platelets, electron microscope studies of, *1139*
Polycythemia
venous-arterial admixture in, 1029-1033
venesection in, *622*
Popliteal aneurysms, *311*
Portacaval anastomosis, *310*
Portal
circulation
in constrictive pericarditis, *1147*
time determinations, *313*
vein thrombosis, *613*
Postcommissurotomy syndrome, *549*
Postpericardiotomy syndrome, 549-555
Posture, orthostatic circulatory disturbances, *473*
Potassium
deficiency, *291*
aldosterone excretion in, *983*
atrial fibrillation in, from acetylcholine, *472*
digitalis affecting myocardium in, *984*
and kidney, *623*
metabolism, and electrocardiography, *1145*
-sodium exchange, *985*
Potassium citrate, arrest of heart with, *1151*
Pregnancy
aortic aneurysms in, *312*
cerebral aneurysms in, *311*
embolic disease in, 1118
after endocarditis, subacute bacterial, 1116
mitral commissurotomy in, 204-207, *988*, 1121
myocardial infarction in, *1143*
protecting against atherosclerosis, *974*
rubella in, and cardiac disorders, 234
in tetralogy of Fallot, *142*
toxemia of
as cardiovascular emergency, 1112
renal biopsies in, *985*
uterine electrolytes in, *306*
Premarin, compared with Manvene, 1035-1040
Pressure pulses, interpretation of, 481-483. *See also* Blood pressure
Procaine amide
effectiveness of, 1116
with quinidine, in atrial fibrillation, *1152*
in ventricular fibrillation with hypothermia, *1151*
Prostatic obstruction, after sedatives, 1119
Protein, C-reactive, in myocardial necrosis, *302*
Prothrombin time
postoperative, *460*
in thrombosis, 492
Protoveratrine, in hypertension, *1147*
Pseudoventricular rhythm, electrocardiography in, *147*
Psychic trauma in hypertension, *616*
Psychosomatic origin of atherosclerosis, 1
Pulmonic valve, *See* Valves
Pulse wave methods of estimating cardiac function, 592, 597
Pulses, interpretation of, 481-483
Pulseless disease, *975*
eye changes in, *311*
Purine nucleotides, synthesis of, in heart muscle extracts, *1151*
Purpura, Schonlein-Henoch, group B-hemolytic streptococcus in etiology of, *306*
Pyelonephritis, hypertension with, 243-248, 693
Pyrogens, intravenous protein-free, 187-197

Quinidine
in atrial fibrillation, 1113
with procaine amide, *1152*
chick embryo heart cells after, *471*
in digitalis toxicity, 1114
long-acting form of, *1153*
mechanism of action of, *1152*
toxic amblyopia from, *618*

Radiation
effects on heart, electrocardiography in, *147*
total irradiation, cardiovascular changes after, *475*
Radioactive plasma protein, lymphatic circulation studies with, *314*
Radioboron uptake, drugs affecting, *152*
Radiocardiography, studies in, *307*
Radioiodine
in angina pectoris, 949
in paroxysmal tachycardia, 900-906
Radiology, after surgery for patent ductus arteriosus, 1047-1054
Radiopotassium, equilibration in edema, *983*
Radiosodium, equilibration in edema, *983*
Rammelkamp lecture, 842-850
Raynaud's disease, 163
sympathectomy in, 5-13
Regitine, effects of, *980*
Regurgitant murmurs, pansystolic, 606
Regurgitation, aortic, detection and estimation of flow, 505-510
Rehabilitation of cardiac patient, 114-126
Renin antibodies, 646, 648-657
Renoprival hypertension, 714-718
Renotrophin causing renal hypertension, 696-700
Resection
in occlusion of aorta or iliac arteries, *442*
in thrombosis, 494
in ventricular aneurysm, *144*

Reserpine
effects of, 208-212
gastric secretion after, *618*
and hexamethonium therapy, *623*
oxygen consumption after, *617*
peripheral action of, *618*
Respiration
carbonic anhydrase activity in disease, *470*
cardiorespiratory syndrome of obesity, *313*
circulatory studies in hyperventilation, *983*
function after mitral commissurotomy, *993*
Respiratory center, sensitivity to carbon dioxide, *981*
Retinal veins, sludging of blood in, *154*
Revascularization, myocardial, *628*
Rhabdomyosarcoma of heart, *990*
Rheumatic fever, *307*, *986*
erythrocyte-sedimentation test in, *986*
steroid therapy in, 1120
streptococcus prophylaxis program, 1112
streptolysis O concentrate affecting, *986*
Rheumatic heart disease, 842-850
endocarditis, subacute, latent, *980*
Scillaren B in, *991*
Rheumatic pulmonary valvular insufficiency, *993*
Rhythm
arrhythmias
in electroconvulsive therapy, *152*
in penetrating heart wounds, 965
atrial gallop rhythm, 1007-1011
baroreceptor responses to acute changes, *304*
ectopic beats, ballistocardiography in, *613*
intermittent parasystole, *467*
postextrasystolic sinus beat, *467*
ventricular gallop in mitral stenosis, *982*
Roentgenkymography in ventricular pre-excitation phenomenon, 225-231
Roentgenology, *307-308*, *624-626*, *986-988*
in aortic sinus aneurysms, unperforated, *625*
of arteries of abdomen and pelvis, *986*
of coronary arteries, *624*
in Eisenmenger complex, *625*
in mitral and aortic insufficiency, *987*
after mitral commissurotomy, *986*
in pericarditis, *224*
of pulmonary artery pressure in mitral valvular disease, *625*
in pulmonary hypertension in mitral stenosis, *986*
in ventricular septal defect, isolated, *626*
Rolicton
diuretic activity of, *472*
effectiveness of, 918-921
Rubella in pregnancy, and cardiac disorders, 234
Rupture of aorta, 1086-1100

Saccharin circulation time, 922-925
Safflower oil, affecting serum lipids, 890-898
Schmitt system of vectorcardiography, 46-54
Schonlein-Henoch purpura, group B-hemolytic streptococcus in etiology of, *306*
Scillaren B in rheumatic heart disease, *991*
Scleroderma, electrocardiography in, 874-880
Sclerosis, pulmonary artery, complicated, *462*
Sedatives, antidiuretic effect of, 1119
Sedimentation rate, erythrocyte in myocardial infaretion, *301*
in rheumatic fever, *986*
Septal defects. *See also* Atria *and* Ventricles
pulmonary stenosis with, arterial oxygen in, *462*
Serotonin, effects of, 208-212
on pulmonary circulation, *472*
on renal hemodynamics, *986*
Shock
renal changes in, treated with levarterenol, *371*
traumatic, cardiac glycosides in, *151*
Shunt
arteriovenous primary, *143*
between systemic artery and left atrium, effects of, *474*
congenital, systolic murmurs in, 608
left-to-right
exercise affecting, *1142*
nitrous oxide test in, 284-290
through high ventricular septal defect, *308*
Signs, physical, *153-154*, *620*, *982*
Silicone clotting time, in alimentary lipemia, 927-934
Sitosterols, effects of, 890-898, 947
Skelton type of hypertension, 768
Sleep, atrial fibrillation in, 1115
Sludging of blood, in retinal veins, *154*
Smoking, effects of
on cardiovascular system, 443-456
factors influencing, *620*
Sodium
depletion, aldosterone excretion in, *983*
excretion
autonomic vasoregulatory reflexes affecting, *983*
in hypertension, 576-581, *1149*, *1150*
intake, in hypertension, *150*, 731, 750-759, 768
plasma levels in hypertension, 761-763
-potassium exchange, *985*
preference threshold of rats in renal hypertension, *469*
Sodium lactate
in bradycardia, *1145*
effects on cardiac function, *305*
effects on renal metabolism in kidney disease, *306*
in Stokes-Adams disease, 325
Sodium nitrite in angina pectoris, 24-36
Sparteine, affecting veratrine response, *152*
Spectrophonocardiography, in murmurs of childhood, *148*
Sphygmography, volumetric, in arterial disease of lower extremities, *468*
Splanchnic circulation in aortic coarctation, *1142*
Splanchnicectomy, in hypertension, 782
Spleen, agenesis of, cardiac abnormalities, 72-83, *142*
Spleen-lung ether time, *313*, *1147*
Staphylococcal pericarditis, acute, *146*
Stenosis
pulmonary artery. *See* Arteries, pulmonary
valvular, 410-417. *See also specific valves*
Steroid therapy in rheumatic fever, 1120
Sterols, affecting serum lipids, 890-898
Stethographic studies in persistent ductus arteriosus Botalli, *466*
Stokes-Adams disease, intravenous drug therapy in, 325-338
Strain obstruction syndrome of femoral vein, *307*
Straining, emphysema response to, 65-70
Streptococcal infections
and rheumatic heart disease, 847
prophylaxis program in rheumatic fever, 1112
and Schonlein-Henoch purpura, *306*
Streptokinase, in thrombosis, 494
Streptolysin O concentrate, effects of, *986*
Stress
blood clotting time and serum cholesterol levels in, 852-860
and coronary artery disease, 1-3
electrocardiography in, 1119
and hypertension, 782
serum lipid changes in, 1117
Stroke, 1123-1135

Stroke volume, 589-599
Strophanthin, effects of, *1153*
Substance P, 669
Substance U, 669
Surgery, *626-628, 988-990*
anesthesia, 292-298
in angina pectoris, 950
aortic, direct vision, *988*
in aortic insufficiency with Marfan's syndrome, *626*
in aortic stenosis, congenital, 1116
in atrial septal defect, *203*
blood vessel replacement, *627*
cardiac arrest, *988, 989*
coagulation in, *461*
commissurotomy, mitral. *See* Commissurotomy, mitral
coronary and carotid artery perfusion in cardiac bypass, *628*
in coronary artery anomaly, 1062-1068
in coronary artery disease, *144*
death after, unusual causes of, *626*
heart-lung apparatus, *989*
in intracranial aneurysms, 1129
in mitral stenosis, indications for, *994*
myocardial revascularization, *628*
in patent ductus arteriosus, radiology after, 1047-1054
postpericardiotomy syndrome, 549-555
in pregnancy, 204-207
preoperative use of digitalis, 1114
in pulmonary venous drainage anomaly with atrial septal defect, *976*
in pulmonic stenosis with intact ventricular septum, 180-185
regression after open pulmonary valvotomy, 862-873
stripping operation in varicose veins, *309*
sympathectomy. *See* Sympathectomy
thoracic, electrocardiogram after, *989*
in thrombosis, 494
in ventricular aneurysm, *144*
in ventricular septal defects, *143*
Suspended heart, syndrome of *149*
Sympatol, effects of, *472*
Sympathectomy
in arterial occlusion, 520
foot blood flow after, *474*
in hypertension with pyelonephritis, 243-248
lumbar, paradoxic gangrene after, *312*
in Raynaud's disease, 5-13
Sympathetic nervous system, affecting blood pressure, 785-789, 798-805
Syphilitic aortitis, bacterial endocarditis with, *1146*
Systole, simulating, at necropsy, 589-599
Systolic murmurs, 601-610

Tachycardia
atrial paroxysmal, with atrioventricular block, *1145*
paroxysmal, radioiodine therapy in, 900-906
pseudoventricular, *147*
ventricular
differential diagnosis of, *467*
drugs for, 1117
Tachyphylaxis, 688
Taussig-Bing complex, *300*
Teeth, and bacterial endocarditis, *616*
Teflon arterial grafts, *627*
Temperature changes after exposure to cold, *621*
Tetraethylammonium
ion transport, *151*
responses to chloride, in hypertension, 785-789
Tetrahydrozoline, action of, *619*
Tetralogy of Fallot, pregnancy with, *142*
Thiamine-deficient baby pigs, electrocardiography in, *618*
Thigh, roentgenology of arteries of, *986*
Thorax
aortography, *987*
cardiothoracic ratio after surgery for patent ductus arteriosus, 1047
electrocardiography after surgery, *989*
pulmonary-thoracic ratio after surgery for patent ductus arteriosus, 1048
Thromboangiitis ogliterans, 21
Thromboelastography, in alimentary lipemia, 927-934
Thromboembolic disease. *See* Coagulation and thromboembolism
Thromboendarterectomy, 494
Thromboplastin, tissue, resistance to, after anticoagulants, *141*
Thyroid gland
in angina pectoris, 949
hormone effects on circulation, *617*
hypothyroidism
and atherogenesis, *1139*
cardiac alterations in, *981*
oxygen consumption in disorders, *617, 620*
radioiodine therapy in paroxysmal tachycardia, 900-906
Toes, ischemic, oscillating bed for, 277-282
Tomovectorcardiography, *979*
Toxemia of pregnancy
as cardiovascular emergency, 1112
renal biopsies in, *985*
Transposition of great vessels, corrected, 249-254
Trauma
cardiac glycosides in traumatic shock, *151*
coronary artery injury, 959
glutamic-oxalacetic transaminase activity in, *145*
nonpenetrating injury of aorta, 1086-1100
penetrating wounds
of aorta, 966-971
of heart, 953-966
pericardial, 960
post-traumatic constrictive pericarditis, *146*
protective action of magnesium in, *621*
retained foreign bodies, 956-959
valvular, 965
Treburon, in thrombosis, 491
Tricuspid valve, *See* Valves
Triethanolamine trinitrate biphosphate in angina pectoris, 24-36
Triglycerides, postprandial effects of eating, *141*
Tromexan therapy
control of, *1140*
in thrombosis, 492
Trypan blue, inducing congenital cardiac anomalies in rats, *300*
Trypsin, in thrombosis, 493
Tuberculosis, and pheochromocytoma, *1148*
Twins, kidney transplants in, 707

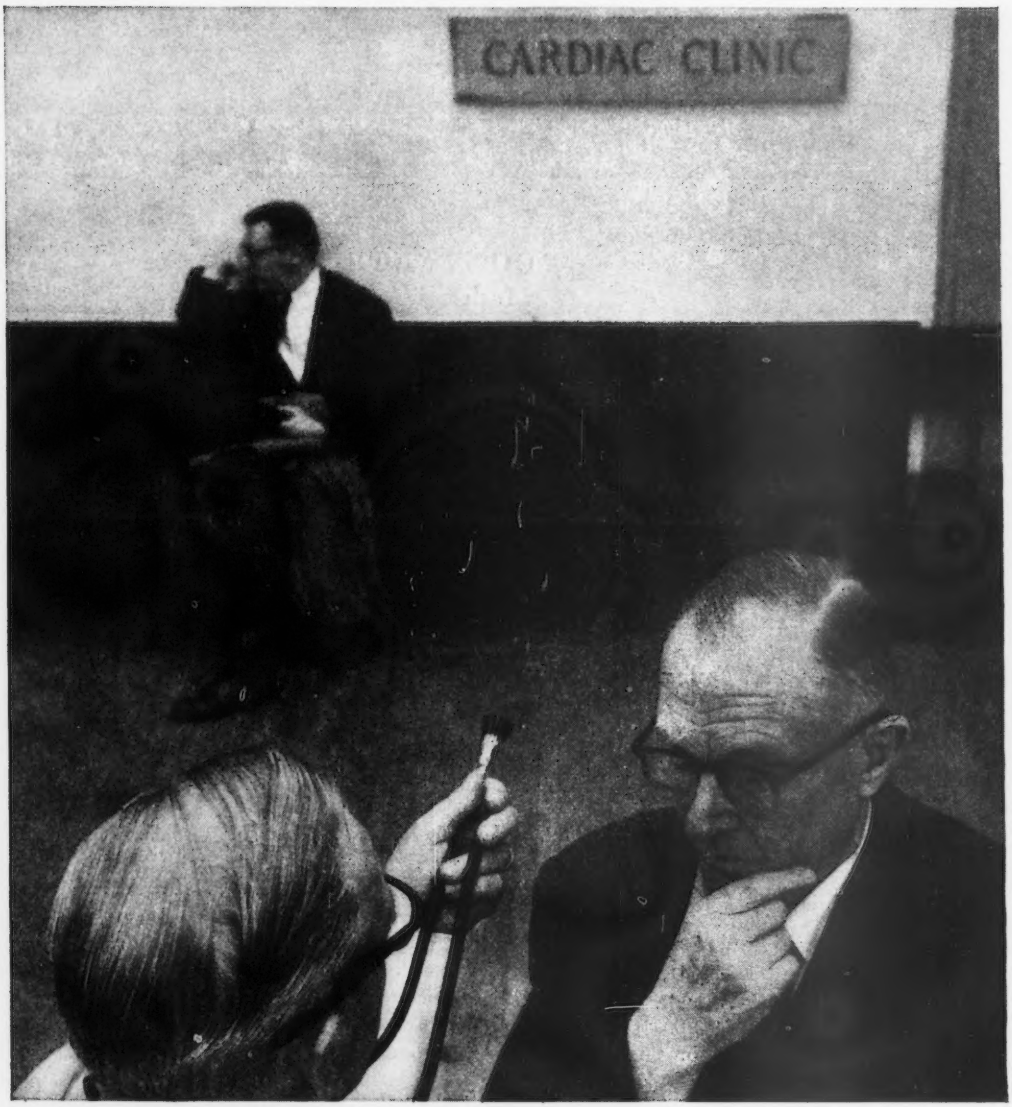
Ulcers, hypertensive ischemic, 163
Uremia, electrocardiography in, *614*
Urine
epinphrine in, *151*
studies in eunuchs, 1076-1084
Urologic aspects of hypertension, 693-695
Uterine electrolytes in pregnancy and labor, *306*

Vagal stimulation, heart block from, ouabain in, *153*
Valsalva, aneurysm of sinus of, with coarctation of aorta and bacterial endocarditis, 432-442
Valsalva's maneuver, 65-70
Valves
aortic
congenital disease, with patent ductus arteriosus, 359-365
experimental, *989*
insufficiency, *991*
aortitis with, *311*
with Marfan's syndrome, repair in, *626*
in rheumatoid arthritis, aortitis with, *911*
roentgenology in, *987*
mitral commissurotomy affecting lesions of, *627*
regurgitant flow measure-

Valves (Cont'd)
ments, 505-510
stenosis, congenital
outlook for children with, *992*
surgery for, 1116
systolic murmurs in disease, 603
disease, *991-994*
rheumatic, 849
injury of, 965
mitral
angina in disease of, *994*
angiocardiography in disease, *307*
anticoagulants in disease, *975*
arial electrokymogram in disease, 213-223, *1145*
arial pressure, left, in disease, 354-358
commissurotomy. *See* Commissurotomy, mitral
diverticulum of, 993
insufficiency
atrial electrokymography in, 213-223, *1145*
confused with tricuspid incompetence, *991*
electrocardiography in, *468*
roentgenology in, *987*
pulmonary artery pressure in disease, roentgen signs of, *625*
regurgitation, systolic murmurs in, 607
stenosis
arterial embolism in, *988*
and epilepsy, *310*
heart sounds in, *466*
hemodynamic abnormalities in, 567-574
hexamethonium affecting, *992*
indication for surgery, *994*
phonocardiography in, *620 978*
pulmonary hypertension in, roentgenology in, *986*
pulmonary ossifications with, *994*
recurrent, *113*
ventilatory response to exercise in, *992*
ventricular gallop in, *982*
pulmonic
insufficiency
experimental, *628*
rheumatic, *993*
stenosis
congenital, survival with, *462*
with intact ventricular septum, 180-185
with patent ductus arteriosus, 232-241
regression after surgery for, 862-873
survival with, *462*
systolic murmurs in disease, 603
stenotic lesions, 410-417
tricuspid
Ebstein's anomaly of, *142*, 543-548, *977*, *1141*
incompetence confused with mitral insufficiency, *991*
liver pulsations in insufficiency, *994*
regurgitation, systolic murmurs in, 608
stenosis, *993*
Valvotomy
mitral. *See* Commissurotomy, mitral
open pulmonary, regression after, 862-873
Varicose veins, stripping operation for, *309*
Vascular disease, 308-313. *See also* Blood vessels
Vascular sling, 418-422
Vasoactive substance, absence of, in coronary sinus blood of dogs, *472*
Vasopressin, 668
Vasoregulatory reflexes, autonomic, effect on sodium and water excretion, *983*
Vectorcardiography
in atrial septal defect, *148*
hypertension affecting, *466*
in myocardial destruction, *147*
orthogonal systems of, 46-54, 1102-1110
polarity convention in, *147*
tomovectorcardiography, *979*
ventricular activation studies, *1144*
in ventricular hypertrophy, *149*
Veins. *See also* Arteriovenous conditions
coronary, catheterization of, complications in, *979*
deep vein ligation in postphlebitic extremity, *310*
femoral, strain obstruction syndrome of, *307*
oxygen saturation of venous blood, *283*
pelvic venography, *309*
portal, thrombosis of, *613*
pulmonary
anomalous drainage with atrial septal defect, *976*
catheterization of, *1145*
total anomalous connection, infradiaphragmatic, 340-347
transposition, with dextrocardia, *462*
retinal, sludging of blood in, *154*
varicose, stripping operation in, *309*
Vena cava constriction
in constrictive pericarditis, *307*
thoracic inferior, aldosterone activity in, *151*
Venesection, effects on pulmonary and cardiac function, *622*
Venous ventricle hypertrophy in dextrocardia, *466*
Ventilation, circulatory studies in hyperventilation, *983*
Ventricle
activation, vectorcardiographic studies, *1144*
aneurysm, reaction for, *144*
conduction disturbances, *621*
defibrillation in coronary occlusion, *270*
electric alternans in single ventricular fibers, *622*
excitation, in experimental bundle-branch block, *979*
force measurements, *621*
gallop, in mitral stenosis, *982*
gradient, ventricular, *147*
left
epinephrine affecting performance of, *1152*
hypertrophy of, electrocardiography in, 255-264
precontracting area, 225-231
right, hypertrophy of
electrocardiography in, *466*
vectorcardiography in, *149*
septum
blood supply of, 391-396
defects
anatomic studies of, 271-275
experimental, *627*
high, complicated, *308*, *462*
in infancy, *1141*
isolated, roentgen signs of, *626*
surgery for, *143*
systolic murmurs in, 608
size of, after surgery for patent ductus arteriosus, 1048
tachycardia, differential diagnosis of, *467*
venous ventricle hypertrophy in dextrocardia, *466*
Ventriculography, cardiac, *625*
Veratrine response, sparteine affecting, *152*
Veratrum alkaloids, *1153*
Veritol, effects of, *472*
Vitamin K, in anticoagulant therapy, 492
Vitamins, effects on cholesterol atherosclerosis, 99-101

Warfarin, in thrombosis, 492
Wassermann test, in endocarditis lenta, *980*
Water excretion
autonomic vasoregulatory reflexes affecting, *983*
in hypertension, 576-581, *1149*, *1150*
Wedge pressure, and pulmonary capillary pressure, 199-203
West Indies, hypertension in, 729
Wolff-Parkinson-White syndrome, ventricular precontracting area in, 225-231
Work capacity, with old myocardial infarction, *464*
Work Classification Clinic, 121

X-rays. *See* Radiation *and* Roentgenology



"Remember him? Used to need injections every week. Since he takes Neohydrin he only comes once a month for check-ups."

oral
organomercurial
diuretic

LAKESIDE

TABLET

NEOHYDRIN®

Prescribe NEOHYDRIN (brand of chlormerodrin) in bottles of 50 tablets.
There are 18.3 mg. of 3-chloromercuri-2-methoxy-propylurea,
equivalent to 10 mg. of non-ionic mercury,
in each tablet.

25058

Circulation

JUNE 1958
VOL. XVII NO. 6

OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

CONTENTS

Index Issue

EDITORIAL

ANOMALOUS CORONARY ARTERIES WITH SPECIAL REFERENCE TO ARTERIOVENOUS-LIKE COMMUNICATIONS. *Jesse E. Edwards* 1001

OBSERVATIONS ON THE MECHANISM OF ATRIAL GALLOP RHYTHM. *James J. Leonard, Arnold M. Weissler and James V. Warren* 1007

OSMOTIC DIURETIC TREATMENT OF REFRACTORY EDEMA. *Lionel M. Bernstein, Bernard Blumberg and Murray C. Arkin* 1013

SERUM LIPIDS IN SOUTH AFRICAN BANTU AND WHITE SUBJECTS. *B. M. Bloomberg, F. Lazarus, Irene Mrost and Rhoda Schneider* 1021

VENOUS-ARTERIAL ADMIXTURE IN THE LUNGS IN PRIMARY AND SECONDARY POLYCYTHEMIA. *James P. Lillehei, Robert L. Johnson, Jr., Nancy Wu, E. Richard Halden and Brian J. Sproule* 1029

SERUM LIPID AND ESTROGENIC EFFECTS OF MANVENE, A NEW ESTROGEN ANALOG: COMPARISON WITH PREMARIN IN MEN WITH CORONARY HEART DISEASE. *William D. Cohen, Norio Higano and Roger W. Robinson* 1035

AN EVALUATION OF BLOOD NITRATE LEVELS. *John W. Berry and Thomas C. Roach* 1041

RADIOLOGIC ASPECTS OF OPERABLE HEART DISEASE: VI. CHANGES FOLLOWING SURGICAL CLOSURE OF PATENT DUCTUS ARTERIOSUS. *Philip Strauss, Herbert L. Abrams and Saul Robinson* 1047

PULMONARY COMPLIANCE IN PATIENTS WITH PERIODIC BREATHING. *Harold A. Lyons, Frank Burno and Richard W. Stone* 1056

ANOMALOUS ORIGIN OF THE LEFT CORONARY ARTERY: THE PHYSIOLOGIC DEFECT AND SUGGESTED SURGICAL TREATMENT. *Robert B. Case, Andrew G. Morrow, Wendell Stainsby and John O. Nestor* 1062

CLINICAL OBSERVATIONS WITH THE FRANK PRECORDIAL LEAD SYSTEM. *J. A. Abildskov, W. W. Street, N. Solomon and A. H. Toomajian* 1069

A COMPARISON OF THE SERUM LIPIDS, LIPOPROTEINS, GLYCOPROTEINS, URINARY 17-KETOSTEROIDS, AND GONADOTROPINS IN EUNUCHS AND CONTROL MALE SUBJECTS. *Robert H. Furman, R. Palmer Howard, M. R. Shetlar, E. Corinne Keaty and Richard Imagawa* 1076

NONPENETRATING TRAUMATIC INJURY OF THE AORTA. *Loren F. Parmley, Thomas W. Mattingly, William C. Manion and Edward J. Jahnke, Jr.* ... 1086

THE NORMAL ORTHOGONAL ELECTROCARDIOGRAM AND VECTORCARDIOGRAM: WITH A CRITIQUE OF SOME COMMONLY USED ANALYTIC CRITERIA. *Hubert V. Pipberger* 1102

PANEL DISCUSSION

PREVENTION AND MANAGEMENT OF CARDIOVASCULAR EMERGENCIES. *Howard B. Sprague, James Metcalfe, Benjamin M. Gasul, Louis A. Soloff, Maurice Sokolow and Stewart G. Wolf, Jr.* 1112

CLINICAL PROGRESS

MANAGEMENT OF SPONTANEOUS INTRACRANIAL SUBARACHNOID HEMORRHAGE. *H. Thomas Ballantine, Jr. and David M. Klein* 1123

ABSTRACTS 1137

AMERICAN HEART ASSOCIATION 1154

CONTRIBUTORS TO THIS ISSUE 1158